CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-928/S-001

Name: CardioTec® (Kit for Preparation of Technetium Tc99m Teboroxime)

Sponsor: Bracco Diagnostics, Inc.

Approval Date: January 9, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-928/S-001

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Approvable Letter	**X**
Labeling	**X**
Division Director's Memo	
Labeling Review	
Medical Review	
Chemistry Reviews	**X**
Environmental Assessment	
Pharmacology / Toxicology Review	
Statistical Review	
Microbiology Review	**X**
Clinical Pharmacology & Biopharmaceutics Review	
Administrative and Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-928/S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-928/SCM-001

Bracco Diagnostics Inc.
Attention: Richard Hunt, Ph.D.
Associate Director, Regulatory Affairs
P.O. Box 5225
Princeton, NJ 08543-5225

Dear Dr. Hunt:

Please refer to your supplemental new drug application dated October 31, 2000, received November 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CardioTec® (Kit for the Preparation of Technetium Tc99m Teboroxime).

We acknowledge receipt of your submissions dated March 12, 2001 and July 6, 2001. Your submission of July 6, 2001, constituted a complete response to our February 28, 2001 action letter.

This supplemental new drug application provides for changes in the formulation to include hydroxypropyl-*y*-cyclodextrin, reduction in NaCl content from 100 mg to 10 mg and an alternative manufacturer and manufacturing site for the Bracco-CardioTec® at Ben Venue Laboratories, and an alternate analytical procedures.

We have completed the review of this supplemental application, and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Patricia A. Stewart, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Eldon E. Leutzinger, Ph.D.
Chemistry Team Leader for the
Division of Medical Imaging and Radiopharmaceutical
Drug Products, (HFD-160)
DNDC II, Office of New Drug Chemistry
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/

Eldon Leutzinger
1/9/02 11:25:18 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-928/S-001

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-928/SCM-001

Bracco Diagnostics Inc.
Attention: Richard J. Hunt, Ph.D.
Associate Director, Regulatory Affairs
P.O. Box 5225
Princeton, NJ 08543-5225

Dear Dr. Hunt:

Please refer to your supplemental new drug application dated October 31, 2000, received November 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CardioTec® (kit for the preparation of Technetium Tc99m Teboroxime).

This supplement proposes minor changes in the formulation and an alternate manufacturer and manufacturing site for CardioTec®

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Specify the acceptable variation in the (b) (4)
2. Submit the applicable methods associated with the (b) (4)
3. Indicate clearly, whether each batch of (b) (4)
4. (b) (4)
5.
6.
7.

Following this page, 1 page withheld in full - (b)(4)

15. Provide the results of the USP extraction tests of the [redacted] (b) (4) stoppers.

In addition, it will be necessary for you to submit final printed labeling (FPL) revised as follows:

1. Since the product stability protocol follows the ICH storage conditions, it is recommended that the storage statement in the package insert, product vial label, and the secondary packaging label be revised to read as follows.

   Store at 25°C(77°F); Excursions permitted to 15-30°C (59-86°F)
   [See USP Controlled Room Temperature]
2. The caution statement in the package insert "Caution: Federal (USA) law prohibits dispensing without prescription" is deleted., but it has not been substituted with the statement "Rx Only". Please add this statement to the package insert.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Patricia A. Stewart, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Eldon E. Leutzinger, Ph.D.
Chemistry Team Leader for the
Division of Medical Imaging and Radiopharmaceutical
Drug Products, (HFD-160)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Eldon Leutzinger
2/28/01 03:47:41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-928/S-001

LABELING

III. LABELING

There have been no labeling changes during this reporting period; labels currently in use are provided in the following table. Representative label samples are provided at the end of this section.

Label Description	Label #	Date Implemented	Summary of Changes
Package Label	CDO-POO	July 2002	First printing from alternate manufacturer *
Vial Label	CDO-VOO	July 2002	First printing from alternate manufacturer *
Box Label	CDO-B00	July 2002	First printing from alternate manufacturer *
Assay Data Label	CDO-S00	July 2002	First printing from alternate manufacturer *

*** S-001, Approved January 9, 2002**

Bracco Diagnostics

CARD-P00

CARDIOTEC®

Kit for the Preparation of Technetium Tc 99m Teboroxime

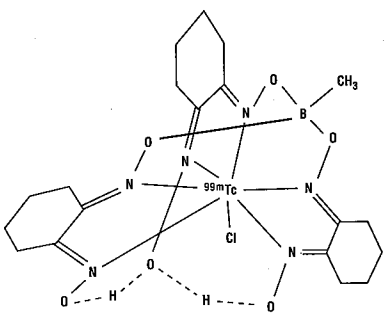
For Diagnostic Use

DESCRIPTION

Each 5 mL reaction vial contains a sterile, nonpyrogenic, lyophilized formulation of 2.0 mg cyclohexanedione dioxime, 2.0 mg methyl boronic acid, 2.0 mg pentetic acid, 9.0 mg citric acid, anhydrous; 10 mg sodium chloride, 45 mg hydroxypropyl gamma cyclodextrin and 0.058 mg (maximum) total tin expressed as stannous chloride ($SnCl_2$), 0.020 mg (minimum) stannous chloride ($SnCl_2$). The pH is adjusted with sodium hydroxide and/or hydrochloric acid prior to lyophilization. The contents of the vial are lyophilized and sealed under nitrogen at the time of manufacture. No bacteriostatic preservative is present.

When sterile, pyrogen-free sodium pertechnetate Tc 99m injection is added to the vial, and the solution is heated at 100° C for 15 minutes, the diagnostic agent Technetium Tc 99m Teboroxime is formed for administration by intravenous injection. The pH of the reconstituted product is 3.7 (range 3.3 to 4.1).

The structure of Tc 99m Teboroxime is shown below:



PHYSICAL CHARACTERISTICS

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours[1]. The principal photon that is useful for detection and imaging studies is listed in Table 1.

TABLE 1

Principal Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

[1]Kocher, David C., "Radioactive Decay Data Tables", DOE/TIC-11026, (1981) p. 108.

External Radiation

The specific gamma ray constant for Tc 99m is 5.4 microcoulombs/kg-MBq-hour (0.78 R/hour-millicurie) at 1 cm. The first half value layer is 0.017 cm of lead (Pb). A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

TABLE 2

Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

To correct for physical decay of Technetium Tc 99m, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

TABLE 3

Physical Decay Chart: Tc 99m half-life 6.02 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0. 447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

*Calibration time

CLINICAL PHARMACOLOGY

Teboroxime is a boronic acid technetium dioxime (BATO) derivative with no known pharmacologic action at the recommended doses.

Following intravenous administration in normal subjects, Technetium Tc 99m Teboroxime was rapidly cleared from the circulation. The mean percent injected dose remaining in the blood at 10 minutes post injection was 10.4 ±4.4%. The injected activity was excreted predominantly through the hepatobiliary system. Cumulative urinary excretion averaged 22 ± 13% through 24 hours.

Myocardial uptake was observed at one minute after Technetium Tc 99m Teboroxime administration, and myocardial images were seen by two minutes post injection. In rabbits and man less than 10% of the Tc 99m following a Technetium Tc 99m Teboroxime injection is protein bound. Clearance from the myocardium was biexponential with approximate biological half-lives of 6 minutes and 13 hours. Substantial uptake was seen in the liver. The following table approximates the effective clearance of Technetium Tc 99m Teboroxime from the heart and liver (based upon data from 2 to 5 subjects).

Time	Heart+	Liver
5 min	2.3%	23%
10 min	1.7%	33%
15 min	1.5%	32%
20 min	1.3%	27%
1 hr	1.1%	24%
2 hr	0.8%	18%
4 hr	0.6%	17%

+Peak heart uptake occurs within 2 min.

INDICATIONS AND USAGE

Technetium Tc 99m Teboroxime is a myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium in patients with suspected coronary artery disease using rest and stress techniques.

CONTRAINDICATIONS

None known.

WARNINGS

Stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate monitoring, resuscitation and support apparatus.

PRECAUTIONS

General

Contents of the reaction vial are intended only for use in the preparation of Technetium Tc 99m Teboroxime and are not to be administered directly to the patient.

Contents of the kit before preparation are not radioactive. However, after the addition of sodium pertechnetate Tc 99m injection, adequate shielding of the final preparation must be maintained.

The components of the kit are supplied sterile and nonpyrogenic. Aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during the addition of the pertechnetate solution and the withdrawal of doses for patient administration.

The Technetium Tc 99m labeling reactions involved in preparing the agent depend on maintaining the stannous ion in the reduced state. Any oxidant present in the sodium pertechnetate Tc 99m supply may thus adversely affect the quality of the radiopharmaceutical. Hence, sodium pertechnetate Tc 99m containing oxidants should not be employed.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to ensure minimum radiation exposure to occupational workers.

Tc 99m Teboroxime should be formulated no more than 8 hours prior to clinical use.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In comparison with most other diagnostic technetium labeled radiopharmaceuticals, the radiation dose to the ovaries (1.8 rads/50 mCi) is high. Minimal exposure [ALARA] is necessary in women of childbearing capability. (See Dosimetry subsection in DOSAGE and ADMINISTRATION section.)

No long-term animal studies have been performed to evaluate carcinogenic potential or to determine the effects of Cardiotec (Kit for the Preparation of Technetium Tc 99m Teboroxime) on fertility in males or females.

Three different mutagenicity assays (a reversion test with bacteria, a chromosomal aberration assay and an *in vivo* mouse micronucleus assay) conducted with cold (decayed) technetium labeled Cardiotec gave negative results. Cardiotec was weakly positive for inducing forward mutations at the TK locus in L5178Y mouse lymphoma cells in the absence of metabolic activation (but only at high concentrations that were toxic to the cells and reduced growth to 33% or less relative to vehicle controls). Cardiotec was negative in this assay in the presence of metabolic activation.

Pregnancy Category C

Animal reproduction studies have not been conducted with Technetium Tc 99m Teboroxime. It is also not known whether Technetium Tc 99m Teboroxime can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Technetium Tc 99m Teboroxime should be given to a pregnant woman only if the expected benefits to be gained clearly outweigh the potential hazards.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, in women of childbearing capability, should be performed during the first few (approximately 10) days following the onset of menses.

Nursing Mothers

Technetium Tc 99m is excreted in human milk during lactation. Therefore, formula feedings should be substituted for breast feedings.

Pediatric Use

Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Uncommon adverse reactions reported in clinical trials include metallic taste in mouth, burning at injection site, facial swelling,

numbness of hand and arm, hypotension and nausea after administration of Technetium Tc 99m Teboroxime.

DOSAGE AND ADMINISTRATION

The suggested adult (70 kg) I.V. single dose of Technetium Tc 99m Teboroxime is 555-1110 MBq (15-30 mCi), with a combined rest/stress study dose of 1295-1850 MBq (35-50 mCi). The dose administered should be the lowest required to provide an adequate study, consistent with ALARA principles. (see Precautions).

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration.

For either rest or stress studies, imaging should begin 2–5 minutes after injection. When used with stress testing, Technetium Tc 99m Teboroxime should be administered while the patient is at maximum stress. The washout kinetics of Technetium Tc 99m Teboroxime requires rapid image acquisition. A substantial amount of the initial myocardial activity is cleared by 20–30 minutes after administration.

If a stress study is to be performed prior to a rest study, it is recommended that an interval of approximately 1.5 hours be allowed for the effects of exercise to dissipate.

If a stress study is to be performed after a rest study, it is only necessary to wait a sufficient amount of time for the residual myocardial activity to clear.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

RADIATION DOSIMETRY

The estimated absorbed radiation doses+ to organs and tissues of an average subject (70 kg) from intravenous injections totaling 1850 MBq (50 millicuries) of Technetium Tc 99m Teboroxime are shown in Table 4.

TABLE 4

Estimated Absorbed Radiation Doses+

	Absorbed Radiation Dose	
Tissue	mGy/1850 MBq	Rads/50 mCi
Brain	6.30	0.63
Gallbladder Wall	48.85	4.89
Small Intestine	33.85	3.39
Upper Large Intestine	61.50	6.15
Lower Large Intestine	43.60	4.36
Heart Wall	10.10	1.01
Kidneys	10.10	1.01
Liver	31.00	3.10
Lungs	14.00	1.40
Spleen	7.45	0.75
Thyroid	5.35	0.54
Ovaries	18.05	1.81
Testes	5.20	0.52
Red Marrow	8.30	0.83
Urinary Bladder Wall	13.70	1.37
Total Body	8.30	0.83

+Method of calculation:

Stabin, M., October 1989, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831.

Assumptions:

6 hour gallbladder emptying interval

2 hour urinary bladder voiding interval

HOW SUPPLIED

Cardiotec® (Kit for the Preparation of Technetium Tc 99m Teboroxime) is supplied as a kit containing 10 reaction vials. Each 5 mL reaction vial contains a sterile, nonpyrogenic, lyophilized formulation of 2.0 mg cyclohexanedione dioxime, 2.0 mg methyl boronic acid, 2.0 mg pentetic acid, 9.0 mg citric acid, anhydrous, 10 mg sodium chloride, 45 mg hydroxypropyl gamma cyclodextrin and 50 µg stannous chloride anhydrous; pH is adjusted with sodium hydroxide and/or hydrochloric acid prior to lyophilization. The contents of the vial are lyophilized and sealed under nitrogen at the time of manufacture.

Kit Contents

10 Vial Kit List No.: 03206

10 sterile 5 mL reaction vials

25 pressure-sensitive labels for Technetium Tc 99m Teboroxime

1 package insert

Preparation

Technetium Tc 99m Teboroxime is prepared with the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure.
2. Place reaction vial in an appropriate lead shield.
3. Swab the rubber closure of the reaction vial with germicide.
4. With a sterile shielded syringe, aseptically obtain and inject 1 mL sterile additive free sodium pertechnetate Tc 99m injection containing 370 to 3700 MBq (10-100 mCi) Tc 99m into the reaction vial. Be sure to maintain a nitrogen atmosphere in the vial by not introducing air during reconstitution. **NOTE:** if sodium pertechnetate Tc 99m injection must be diluted for use with Cardiotec (Kit for the Preparation of Technetium Tc 99m Teboroxime), only preservative free Sodium Chloride Injection USP should be used.
5. Swirl the contents of the vial for a few seconds and then heat the vial in a water bath or heating block at 100 ± 2° C for 15 ± 1 minutes and cool to room temperature.
6. Using proper shielding, the vial contents should be visually inspected. Use only if the solution is clear and free of particulate matter and discoloration.
7. Assay the reaction vial using a suitable radioactivity calibration system. Record the Technetium Tc 99m concentration, total volume, assay time and date, expiration time and lot number on the vial shield label and affix the label to the shield.
8. Store the reaction vial containing the Technetium Tc 99m Teboroxime at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [See USP Controlled Room Temperature] until use; at such time the product should be aseptically withdrawn. Technetium Tc 99m Teboroxime should be used within 8 hours of preparation.

NOTE: Adherence to the above product reconstitution instructions is recommended.

Product should be used within 8 hours after preparation.

Final product with radiochemical purity of at least 90% was used in clinical trials that established safety and effectiveness. The radiochemical purity was determined by the following method.

Radiochemical Purity Tests Methods

Percent Reduced Hydrolyzed Tc 99m

Materials

Stationary Phase—Whatman 31 ET Chrom chromatography paper, precut to 1.3 cm x 11.0 cm. Mark the individual strip using a pencil such that the origin and solvent front are located 2.0 and 9.0 cm respectively from the bottom. Also make a mark for cutting at 4.0 cm from the bottom.

Mobile Phase—Freshly prepare a 50:50 v/v solution of 0.9% NaCl/acetone. Fill the chromatography chamber with this solution to a height of 1 cm.

Method

1. Spot approximately 5µL (drop from a 25–27 g needle) of Tc 99m Teboroxime at the origin of the strip.
2. Immediately develop in the NaCl/acetone solution to the 9 cm mark.
3. Remove the strip and allow to air dry.
4. Cut the strip at the cutting mark (4.0 cm).
5. Assay each segment for radioactivity and calculate the percentage of Reduced-Hydrolyzed Tc 99m using the following equation:

$$\% \text{ Reduced-Hydrolyzed Tc 99m} = \% A = \frac{\text{Radioactivity of bottom segment}}{\text{Radioactivity of top + bottom segments}} \times 100$$

Percent Soluble Tc 99m Contaminants

Materials

Stationary Phase—Whatman 31 ET Chrom chromatography paper, precut to 1.3 cm x 11.0 cm. Mark the individual strip using a pencil such that the origin and solvent front are located 2.0 and 9.0 cm respectively from the bottom. Also make a mark for cutting at 6.5 cm from the bottom. The strip needs to be impregnated with NaCl prior to use. Place the strip in a saturated NaCl solution and allow the strip to soak for two minutes. Remove the strip and allow the strip to air dry.

Mobile Phase—Use a 0.9% NaCl Solution. Fill the chromatography chamber with this solution to a height of 1 cm.

Method

1. Spot approximately 5µL (drop from a 25-27 g needle) of Tc 99m Teboroxime at the origin of the strip.
2. Immediately develop in the 0.9% NaCl Solution to the 9 cm mark.
3. Remove the strip and allow to air dry.
4. Cut the strip at the cutting mark (6.5 cm)
5. Assay each segment for radioactivity and calculate the percentage of soluble Tc 99m contaminants using the following equation:

$$\% \text{ Soluble Tc 99m Contaminants} = \% B = \frac{\text{Radioactivity of top segment}}{\text{Radioactivity of top + bottom segments}} \times 100$$

% RADIOCHEMICAL PURITY = 100–(%A + %B)

Storage

Store the kit as supplied at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [See USP Controlled Room Temperature] prior to and following reconstitution. Use within 8 hours of reconstitution.

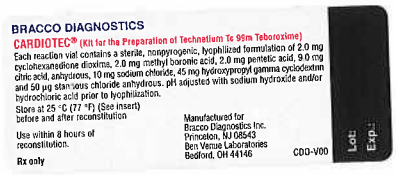
The U.S. Nuclear Regulatory Commission has approved this reagent kit for distribution to persons licensed to use byproduct material identified in §35.200 of 10 CFR Part 35, to persons who hold an equivalent license issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

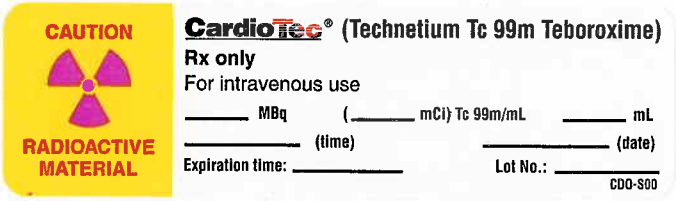
Rx only

Manufactured for:
Bracco Diagnostics Inc.
Princeton, NJ 08543

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

CARD-P00 Printed in USA Revised May 2002


BRACCO DIAGNOSTICS
CARDIOTEC® (Kit for the Preparation of Technetium Tc 99m Teboroxime)
Each reaction vial contains a sterile, nonpyrogenic, lyophilized formulation of 2.0 mg cyclohexanedione dioxime, 2.0 mg methyl boronic acid, 2.0 mg pentetic acid, 9.0 mg citric acid, anhydrous, 10 mg sodium chloride, 45 mg hydroxypropyl gamma cyclodextrin and 50 µg stannous chloride anhydrous. pH adjusted with sodium hydroxide and/or hydrochloric acid prior to lyophilization.
Store at 25 °C (77 °F) (See insert) before and after reconstitution
Use within 8 hours of reconstitution.
Rx only
Manufactured for Bracco Diagnostics Inc. Princeton, NJ 08543 Ben Venue Laboratories Bedford, OH 44146
CDO-V00
Lot:
Exp.:


CAUTION
RADIOACTIVE MATERIAL
CardioTec® (Technetium Tc 99m Teboroxime)
Rx only
For intravenous use
_____ MBq (_____ mCi) Tc 99m/mL _____ mL
_____ (time) _____ (date)
Expiration time: _____
Lot No.: _____
CDO-S00


10 vials
INTRAVENOUS • DIAGNOSTIC
List 03206
CardioTec®
Kit for the Preparation of Technetium Tc 99m Teboroxime
Rx only
Store at 25° C (77° F) [See insert] before and after reconstitution.
Use within 8 hours after reconstitution.
For Technical Information
Call: 1-800-257-5181
BRACCO DIAGNOSTICS
CardioTec®
NONRADIOACTIVE
Kit for the Preparation of Technetium Tc 99m Teboroxime
Each reaction vial contains a sterile, nonpyrogenic, lyophilized formulation of 2.0 mg cyclohexanedione dioxime, 2.0 mg methyl boronic acid, 2.0 mg pentetic acid, 9.0 mg citric acid, anhydrous, 10 mg sodium chloride, 45 mg hydroxypropyl gamma cyclodextrin and 50 µg stannous chloride anhydrous. pH adjusted with sodium hydroxide and/or hydrochloric acid prior to lyophilization. Vial contents are sealed under nitrogen at time of manufacture.
Dosage: See insert
Manufactured for
Bracco Diagnostics Inc.
Princeton, NJ 08543
by Ben Venue Laboratories, Inc.
Bedford, OH 44146
Made in USA CDO-B00
LOT
EXP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-928/S-001

CHEMISTRY REVIEW

CHEMIST'S REVIEW	1.ORGANIZATION **HFD-160**	2. NDA Number(s) 19-928
3. Name and Address of Applicant (City & State): Bracco Diagnostics Inc. P. O. Box 5225 Princeton, NJ 08543-5225		4. AF No. 5. Supplement(s) Number(s) Date(s) SCM-001 10/31/00
6. Drug Name: CardioTek®	7. Nonproprietary Name: Kit for the preparation of Technetium Tc99m Teboroxime	8. Amendments & Other (reports, etc) - Dates
9. Supplement Provides For: Changes in the formulation to include hydroxypropyl-g-cyclodextrin instead of γ-cyclodextrin, reduction in NaCl content from 100 mg to 10 mg and an alternate manufacturer and manufacturing site for the Bracco-CardioTek® at Ben Venue Laboratories, and alternate analytical procedures.		
10. Pharmacological Category: Radiopharmaceutical	11. How Dispensed: ☒ Rx ☐ OTC	12. Related IND(s)/ NDA(s)/DMF(s)
13. Dosage Form(s): Solution	14. Potency(ies): ~20 mCi	
15. Chemical Name and Structure: Technetium Tc99m Teboroxime		16. Records/Reports Current:☒ Yes ☐ No Reviewed: ☒ Yes ☐No
17. Comments: This is a prior-approval supplement seeking multiple changes. The original product has been reformulated to improve the appearance of the reconstituted product by replacing γ- cyclodextrin (50 mg/vial) with the more soluble 2-hydroxypropyl-γ-cyclodextrin (45 mg/vial) and by reducing the sodium chloride content from 100 mg/vial to 10 mg/vial. The manufacturing facility is changed from Squibb to Ben Venue Laboratories. The (b) (4) rubber stoppers are replaced with the (b) (4) stoppers. The analytical procedure for (b) (4) is changed from (b) (4) to (b) (4)		
18. Conclusions and Recommendations: The OC recommended approval of the Ben Venue Laboratories facility on 01/30/01. Since (b) (4) testing facility was not inspected in connection with this supplement, the applicant should provide certification that this facility is in compliance with current good manufacturing practices and also should inform when the facility was inspected in the past. Until this issue is resolved, the radiochemical purity testing should be continued at the approved Bracco facility. The microbiology reviewer recommended "approval" from the point of product quality-microbiology. However, many issues were noted under CMC. The raw material test methods should be provided. The closure system should be evaluated from the point of (b) (4) (b) (4). The USP extraction results of the two stoppers should be submitted. Analytical procedures for (b) (4) need additional improvements. The proposed (b) (4) Some changes in the labeling are needed. The supplement is "approvable" from the point of CMC, pending resolution of the deficiencies identified in this review. The listed deficiencies should be communicated to the applicant. CC: Original NDA# 19-928 HFD-160/Division File HFD-160/Chemist/Harapanhalli HFD-160/CSO/StewartP R/D initialed by : Leutzinger		
19. REVIEWER		
Name Ravi S. Harapanhalli, Ph.D.	Signature	Date Completed February 23, 2001

Following this page, 36 pages withheld in full - (b)(4)

/s/

Ravi Harapanhalli
2/27/01 11:15:55 AM
CHEMIST

Eldon Leutzinger
2/27/01 12:35:09 PM
CHEMIST

CHEMIST'S REVIEW	1.ORGANIZATION **HFD-160**	2. NDA Number(s) **19-928**
3. Name and Address of Applicant (City & State): Bracco Diagnostics P.O.Box 5225 Princeton, NJ 08543-5225		4. AF No. 5. Supplement(s) Number(s) Date(s) SCM-001 10/13/00
6. Drug Name: CardioTek•	7. Nonproprietary Name: Kit for the preparation of Technetium Tc99m Teboroxime	8. Amendments & Other (reports, etc.) - Dates AC- 06-Jul-01
9. Supplement Provides For: Changes in the formulation to include hydroxypropyl-γ-cyclodextrin instead of γ-cyclodextrin, reduction in NaCl content from 100 mg to 10 mg and an alternate manufacturer and manufacturing site for the Bracco-CardioTek• at Ben Venue Laboratories, and alternate analytical procedures.		
10. Pharmacological Category: Radiopharmaceutical	11. How Dispensed: • Rx • OTC	12. Related IND(s)/ NDA(s)/DMF(s)
13. Dosage Form(s): Solution	14. Potency(ies):	
15. Chemical Name and Structure: Technetium Tc-99m Teboroxime		16. Records/Reports Current: •Y es • N o Reviewed: • Yes •N o
17. Comments: The OC has recommended acceptable for BVL on 1/30/01.		
18. Conclusions and Recommendations: The sponsor has sufficiently satisfied the chemistry concerns and the supplement is recommended for "approval". All the items listed under "supplement provides for" should be listed in the action letter. The sponsor should submit the final printed labeling when it becomes available. CC: Original NDA# 19-928 HFD-160/Division File HFD-160/Chemist/Kasliwal HFD-160/PM/Stewart R/D initialed by : Leutzinger		
19. REVIEWER		
Name Ravindra K. Kasliwal, Ph.D.	Signature	Date Completed 08-Jan-02

REVIEW NOTES

The original supplement submission was reviewed by Dr. R.S. Harapanhalli and was determined to be "approvable" pending resolution of several deficiencies. These deficiencies were sent to the sponsor in an approvable letter dated 28-Feb-2001. This major amendment dates 07-Jul-2001 is submitted to response to those deficiencies. Below, the deficiencies have been listed, followed by the sponsor's response. My evaluation follows the sponsor's response.

(b) (4)

Following this page, 4 pages withheld in full - (b)(4)

(b) (4)

DEFICIENCY:

In addition, it will be necessary for you to submit final printed labeling (FPL) revised as follows:

1. *Since the product stability protocol follows the ICH storage conditions, it is recommended that the storage statement in the package insert, product vial label, and the secondary packaging label be revised to read as follows.*
   Store at 25°C (77°F); Excursions permitted to 15-30°C (59-86°F)
   [See USP Controlled Room Temperature]

2. *The caution statement in the package insert "Caution: Federal (USA) law prohibits dispensing without prescription" is deleted. but it has not been substituted with the statement "Rx Only". Please add this statement to the package insert.*

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the 'changes that are being made.

RESPONSE:

On the labels, the sponsor has placed the statement "Store at 25°C (77°F) [see insert]" and the statement in the insert has been amended to "Store the kits as supplied at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]". Reviewer's comments: These statements are acceptable.

The statement "Rx Only" has been added to the primary, secondary packaging labels as well the package insert.

REVIEWER'S COMMENTS: The comments have been adequately addressed.

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
1/8/02 02:31:15 PM
CHEMIST

Eldon Leutzinger
1/8/02 02:34:54 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-928/S-001

MICROBIOLOGY REVIEW

REVIEW TO HFD-160
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW #1 OF NDA

8 February 2001

A. 1. NDA: 19-928/SCM-001

2. TYPE OF SUPPLEMENT: Prior Approval

3. SUPPLEMENT PROVIDES FOR: An alternate manufacturing site, a change from [redacted] (b) (4) to [redacted] (b) (4), and a change to the rubber stopper.

4. APPLICANT/SPONSOR: Bracco Diagnostics, Inc.
PO Box 5225
Princeton, NJ 08543-5225

5. MANUFACTURING SITE: Ben Venue Laboratories
300 Northfield Road
Bedford, Ohio 44146
Estab # 1519257

6. DRUG PRODUCT NAME:
Proprietary: CardioTec
Nonproprietary: Kit for the preparation of Tc 99m Teboroxime
Drug Priority Classification: P

7. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Kit for Intravenous Administration

8. METHOD(S) OF STERILIZATION: [redacted] (b) (4)
9. PHARMACOLOGICAL CATEGORY: Imaging Agent

B. 1. DOCUMENT/LETTER DATE: October 31, 2000
2. RECEIPT DATE: November 1, 2000
3. CONSULT DATE: November 1, 2000
4. DATE OF AMENDMENT: N/A
5. ASSIGNED FOR REVIEW: December 7, 2000
6. SUPPORTING/RELATED DOCUMENTS:

C. REMARKS: The drug product is not currently being marketed

D. CONCLUSIONS: This submission is recommended for approval from the standpoint of product quality microbiology.

Bryan S. Riley, Ph.D.
Microbiology Reviewer

cc.: Original NDA 19-928
HFD 160/Division File
HFD 160/Project Manager
HFD 160/Other
HFD 805/Consult File
HFD 805/ B. Riley

Drafted by: Bryan Riley, Ph.D.
R/D initialed by: Peter Cooney, Ph.D.

filename: C:\Data\Data\Word\NDA\S\19928s1.doc

E. REVIEW NOTES:

1. General Drug and Processing Descriptions.

Ingredient	Amount/Vial
Cyclohexanedione Dioxime	2.0 mg
Methyl Boronic Acid	2.0 mg
Penteic Acid	2.0 mg
Citric Acid Anhydrous	9.0 mg
Stannous Chloride, Anhydrous	0.05 mg
Sodium Chloride	10.0 mg
Hydroxypropyl Gamma Cyclodextrin	45.0 mg
Sodium Hydroxide	pH adjustment
Hydrochloric Acid	pH adjustment
Nitrogen	q.s.
(b) (4)	

The vials, stoppers, and (b) (4) equipment are sterilized. (b) (4) The manufacturing method is basically the same as in the approved application.

ADEQUATE

2. Manufacturing and Product Flow.

(b) (4)

ADEQUATE

3. Facility and Environmental Control Descriptions.

(b) (4)

Following this page, 5 pages withheld in full - (b)(4)

/s/

Bryan Riley
2/13/01 02:21:19 PM
MICROBIOLOGIST

Peter Cooney
2/13/01 03:37:25 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-928/S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA NO. 19928 REF. NO. 001

NDA SUPPL FOR Scm

ORIGINAL

BRACCO DIAGNOSTICS

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

Shay Panchalla
approvable
02/23/01

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 0 1 2000
HFD-160

October 31, 2000

NDA 19-928

Food and Drug Administration
Center for Drug Research and Evaluation
Office of Drug Evaluation III
Document Control Room 18B-03
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Eldon Leutzinger, Ph.D., Chemistry Team Leader, DNDCII
Division of Medical Imaging and Radiopharmaceutical Drug Product
(HFD-160)

Dear Dr. Leutzinger:

Reference is made to our approved NDA # 19-928 for CardioTec® (Kit for the preparation of Technetium Tc-99m Teboroxime). Pursuant to 21 CFR 314.70(b)(2)(i) and (vi), we are hereby submitting a supplement, which provides for minor changes in the formulation and an alternate manufacturer and manufacturing site to the above referenced NDA.

In support of this submission, we are providing the following information in 3 volumes:

Volume 1
Introduction and Summary
Component and Composition Statement
Raw Material Controls
Manufacturing Site Information and Certifications
Manufacturing Batch Records and In-Process Testing

Volume 2
Sterility Assurance Package

Volume 3
Packaging Components
Drug Product Quality Control and Specifications
Stability
Labeling

A copy of this application is being submitted in parallel to the Newark District Preapproval Inspection Manager at the North Brunswick, New Jersey, office.

Should you have any questions or comments regarding this submission, please contact the undersigned at (609) 514-2439.

Sincerely,

Richard J. Hunt, Ph.D.
Associate Director, Regulatory Affairs

Food and Drug Administration
Rockville MD 20857

NDA 19-928/S-001

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

NOV 3 2000

Attention: Richard J. Hunt, Ph. D.
Associate Director

Dear Dr. Richard:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Cardio Tec
NDA Number:	19-928
Supplement Number:	S-001
Date of Supplement:	October 31, 2000
Date of Receipt:	November 01, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 31, 2000, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical
Drug Products, HFD-160
Office of Drug Evaluation III
Attention: Document Control Room 18B-06
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

11/2/2000

Kyong Cho, Pharm. D.
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

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

March 12, 2001

NDA 19-928/SCM-001

ORIGINAL
SCM-001
BC

NDA SUPP AMEND

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Document Control Room 18B-06
5600 Fishers Lane
Rockville, MD 20857

Attention: Eldon Leutzinger, Ph.D., Chemistry Team Leader
Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160)

Dear: Dr. Leutzinger:

Reference is made to our supplemental new drug application for CardioTec® (Kit for the Preparation of Technetium Tc99m Teboroxime) NDA 19-928/SCM-001, dated October 31, 2000 which provides for minor changes in the formulation and an alternate manufacturer and manufacturing site. Further reference is made to your letter dated February 28, 2001 wherein you stated the supplement is approvable, pending receipt and acceptance of additional information.

Pursuant to 21 CFR 314.120(a)(1), we are notifying you of our intent to amend the supplemental application. The responses to your comments will be addressed to you shortly.

Please contact the undersigned at 609-514-2254 if you have any questions.

Sincerely,

MBenson

Melanie Benson
Director, US Regulatory Affairs.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

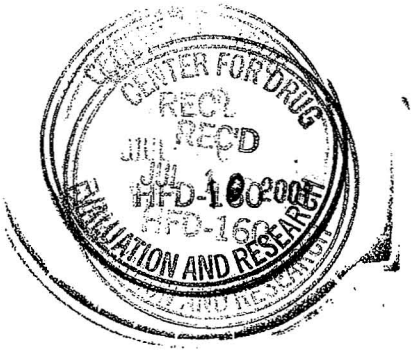
CSO INITIALS DATE 3/14/01

BRACCO GROUP
Tel 800-631-5245 Fax 609-514-2425

ORIGINAL

SCM 001

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



July 6, 2001

NDA 19-928/SCM-001

Food and Drug Administration
Center for Drug Research and Evaluation
Office of Drug Evaluation III
Document Control Room 18B-03
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Eldon Leutzinger, Ph.D., Chemistry Team Leader, DNDCII
Division of Medical Imaging and Radiopharmaceutical Drug Product
(HFD-160)

Dear Dr. Leutzinger:

Reference is made to our supplemental new drug application for CardioTec® (Kit for the Preparation of Technetium Tc99m Teboroxime) NDA 19-928/SCM-001, dated October 31, 2000 which provides for minor changes in the formulation and an alternate manufacturer and manufacturing site. Further reference is made to your letter dated February 28, 2001 wherein you stated the supplement is approvable, pending receipt and acceptance of additional information.

Attached are the responses to the areas of concern.

Should you have any questions or comments regarding this submission, please contact the undersigned at (609) 514-2439; fax (609) 514-2539.

Sincerely,

Richard J. Hunt, Ph.D.
Associate Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-928/SCM-001

Bracco Diagnostics Inc.
Attention: Richard J. Hunt, Ph.D.
Associate Director, Regulatory Affairs
P.O. Box 5225
Princeton, NJ 08543-5225

Dear Dr. Hunt:

We acknowledge receipt on July 10, 2001, of your July 6, 2001, resubmission to your supplemental new drug application for CardioTec (Kit for the Preparation of Technetium Tc99m Teboroxime).

This resubmission contains additional information submitted in response to our February 28, 2001 action letter.

With this amendment, we have received a complete response to our February 28, 2001 action letter.

If you have any questions, call Patricia A. Stewart, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Kyong Cho, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Radiopharmaceutical Drug Products
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 Cho
7/17/01 04:47:37 PM