CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75392

BIOEQUIVALENCY REVIEW(S)

5

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

ANDA # 75-392 **SPONSOR : Gensia Scior Pharmaceuticals**
DRUG & DOSAGE FORM : Propofol Injectable Emulsion
STRENGTH(s) : 10 mg/mL; 20 mL prefilled syringe
TYPE OF STUDY: **SD** **SDF** **MULT X OTHER**

Formulation is acceptable

Waiver is granted

PRIMARY REVIEWER : Jahnavi S. Kharidia BRANCH :3
INITIAL : /S/ **DATE :** 11/6/98

Team Leader : Barbara M. Davit BRANCH : 3
INITIAL : /S/ **DATE :** 11/6/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL : _____ **DATE :** 11/9/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL : _____ **DATE :**

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-392 APPLICANT: Gensia Sicor Pharmaceuticals

DRUG PRODUCT: Propofol Injectable Emulsion
10 mg/mL; 20 mL prefilled syringe

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Propofol Injectable Emulsion
10 mg/mL; 20 mL prefilled syringe
ANDA# 75-392
Reviewer: Jahnavi S. Kharidia
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Gensia Scior Pharmaceuticals, Inc.
Irvine, CA
Submission Date:
May 29, 1998

Addendum to the October 30, 1998 Review

Recommendation:

Gensia's formulation for Propofol Injectable Emulsion, 10 mg/mL, contains 0.025% sodium metabisulfite instead of 0.005% disodium edetate used in the Diprivan® Injectable, 10 mg/mL, manufactured by Zeneca Laboratories. The application is acceptable based on CFR 320.24(b)(6). Therefore, Gensia Laboratories' Propofol Injectable Emulsion, 10 mg/mL is deemed bicequivalent to Diprivan® Injectable, 10 mg/mL, manufactured by Zeneca Laboratories.

/S/
Jahnavi S. Kharidia, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT BMD 4/5/99
FT INITIALLED BDAVIT /S/ Date: 4/12/99

Concur: /S/ Date: 4/14/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA #75-392, original, Kharidia, Davit, Drug File, Division File

Please enter as US document

OTHER AC

Propofol Injectable Emulsion
10 mg/mL; 20 mL prefilled syringe
ANDA # 75-392
Reviewer: Jahnavi S. Kharidia
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Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine CA 92618
Submission Date:
May 29, 1998

Review of a Waiver Request

Background

The applicant received a waiver for its Propofol Injection, 10 mg/mL in 20 mL, 50 mL and 100 mL vials (ANDA submission date=12/24/96; review date=5/16/97). Formulation for ANDA is identical to the reference formulation containing 0.005% EDTA. ANDA is still pending.

The use of 0.005% EDTA infringes the patent held by Zeneca. Therefore, the firm reformulated its Propofol Injection (with 0.025% sodium metabisulfite) and submitted a waiver request for Propofol Injectable Emulsion, 10 mg/mL in 20 mL, 50 mL and 100 mL vials (ANDA #75-102; submission date=1/16/98). ANDA 75-102 discloses that the firm wants to withdraw the 20 mL prefilled syringe and replace it with Propofol Injectable Emulsion, 10 mg/mL in 20 mL, 50 mL and 100 mL vials. ANDA #75-102 with 0.025% sodium metabisulfite was sent to Dr. McCormick (HFD-170) for a consultation. OGD is presently reviewing the result of the consult.

The firm is now submitting a waiver request for its Propofol Injectable Emulsion, 10 mg/mL, in a 20 mL prefilled syringe. The formulation of prefilled syringe is the same as that reported in ANDA# 75-102. The listed reference drug is Diprivan® 1% Injectable Emulsion (10 mg/mL propofol) by Zeneca Pharmaceuticals.

Comments

1. The new formulation is different from the reference product as shown in Table 1. Dr. McCormick has evaluated the safety and stability issues of the formulation. Her evaluation is under review by OGD.

Table 1. Formulation Comparison **[Not To Be Released Under FOI]**

Ingredients	Test Formulation (mg/mL)	Reference Formulation (mg/mL)
Propofol	10	10
Soybean Oil	100	
Glycerin	22.5	
Egg Lecithin	12	
Sodium Metabisulfite	0.025%	
Sodium Hydroxide	qs to pH	

2. Besides the preservative system, the test product differs from the reference product in the pH specifications. Gensia showed that the physical properties (density, osmality and viscosity) of the test and reference products are equivalent.

Table 2: Comparison of Physical Properties

Physico-Chemical Properties	Test Formulation	Reference Formulation
Appearance		
Density		
Osmolality, mOsm/kg		
Viscosity, centistokes		

3. The globule size distribution of the test and reference drug products was determined. Two different instruments were used :

The results are summarized in Attachment A.

The total number of particles ranging from μm in size is very similar for both products. The number of particles in the particle size range of μm shows more variability between test and reference products. Two lots of the innovator's product filled in a syringe (lot # 8042w vs. lot # 3206A) display different large particle size distribution (Please see vol. 1.1, pages # 100050 - 100053).

4. The pH of test product does not impact the physical properties and the particle size distribution.

5. A waiver for the test product will be granted pending the acceptance of the new formulation by OGD after reviewing the consult by Dr. McCormick (Attachment B).

Recommendation

The Division of Bioequivalence agrees that the information submitted by Gensia demonstrates that its Propofol Injectable Emulsion with 0.025% sodium metabisulfite, 10 mg/mL in 20 mL prefilled syringe, falls under 21 CFR 314.94(a)(9)(iii) of the

Bioavailability/Bioequivalence Regulations. However, granting the waiver is pending the acceptance of the new formulation by OGD.

/S/

Jahnavi S. Kharidia, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED BDAVIT BMD 9/18/98
FT INITIALED BDAVIT /S/ 9/21/98

Concur: /S/ Date: 10/2/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA # 75-392 (original, duplicate), Kharidia, HFD-658, Drug File, Division File