CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75392

CORRESPONDENCE

ANDA 75-392

Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Lowe
17 Hughes
Irvine, CA 92618

JUN 26 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your faxed correspondence dated June 23, 1998.

NAME OF DRUG: Propofol Injection, 10 mg/mL

DATE OF APPLICATION: May 29, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 1, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

GensiaSicor™
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August 21, 2000

NEW CORRESP
NC
Not sued w/in 45 days!
8/29/00

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion
10 mg/mL, Pre-filled Syringe
ANDA 75-392

PATENT AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Reference is also made to the amendment dated June 21, 2000, which contained a Paragraph IV Patent Certification Statement for U.S. Patent No. 5,908,869.

As required under CFR 314.107 (f)(2) in regard to Patent No. 5,908,869, we wish to inform the Agency that neither Gensia Sicor nor its legal representatives have been served with a legal complaint as a result of our Notice of Certification received by Zeneca, Ltd. To the best of our knowledge, we are not aware of any legal action taken within the requisite 45 days that expired on August 19, 2000.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment or you require further clarification, please do not hesitate in contacting me at (949) 457-2808. I may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

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CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 22 2000
OGD

cc: Ms. Elizabeth Kezille
Acting District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

GensiaSicor™
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March 7, 2000

NDA ORIG AMENDMENT
N/FA

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL
ANDA 75-392

FACSIMILE AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Reference is also made to our amendments dated June 24 and December 22, 1998 and May 7, August 30 and November 12, 1999. Further reference is made to the Agency's facsimile dated March 1, 2000.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional **chemistry** information as requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808. I may also be contacted by facsimile at (949) 583-7351.

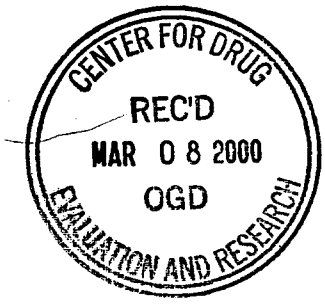
Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

H:\DATA\IRG\PRO75392\AMENDS\Amend9.doc

cc: Mr. Thomas Sawyer
Acting District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715



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GensiaSicor™
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May 22, 2000

ORIG AMENDMENT
N/FA

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL
ANDA 75-392

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Reference is also made to the telephone conversations between Mr. Ray Brown, Chemistry Reviewer; Mr. Mark Anderson, Project Manager; as well as Dr. Villayat Sayeed, Deputy Director, Chemistry Division II; and myself on May 17, 2000. During the teleconferences, additional FDA comments were provided with regard to the stability program for the product.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide a response to the Agency's comments from the teleconferences on May 17, 2000.

First, the Agency requested that Gensia Sicor comply with either FDA stability guidance or the ICH stability guidelines, and set the upper temperature limit for the stability program to either 25 ± 5°C as specified in the FDA guidance or 15°C - 30°C as specified in the ICH guideline. In response to this request, Gensia Sicor elects to maintain the upper limit of the storage temperature at 22°C. Our rationale is as follows:

1) This upper limit was set to comply with the labeled storage condition of the reference listed drug, AstraZeneca's Diprivan (NDA 19-627, approved [illegible]

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MAY 24 2000
OGD

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
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Agency on June 11, 1996). A copy of the side-by-side comparison showing identical label storage conditions for Gensia Sicor and AstraZeneca included in the original application on pages 100034, 100035 and 100039 is provided in **Attachment 1** for your reference. Since the conditions of AstraZeneca's stability program represents proprietary information and is unavailable for public review, we have surmised that AstraZeneca optimized the temperature conditions to assure both the chemical and physical stability of their product. Otherwise for ease of marketing their product, AstraZeneca would have claimed a standard room temperature condition for storage instead of the current, non-standard range defined in the Diprivan labeling.

2) In addition, Gensia Sicor deferred to the experience of AstraZeneca in their knowledge of the stability of this specific product and consciously matched the current labeled storage condition for the generic with that of the reference listed drug.

3) The FDA stability guidance (under the section heading "Stability Testing for New Drug Applications") and ICH guidelines include provisions for lower storage conditions as in the case of suspensions and emulsions (refer to page 8 and 6/13, "Storage Test Conditions," respectively.) Therefore, both FDA and ICH recognized that standard storage conditions may not be applied to all products. Since Propofol is an emulsion product, Gensia Sicor, as well as the innovator, AstraZeneca, addressed both the physical stability and the chemical stability when establishing the storage test conditions, therefore, our position is in accordance with both FDA and ICH provisions.

4) Furthermore, the stability program established for Propofol in the prefilled syringes is identical to the stability programs for Propofol under ANDA 75-102 (approved by the Agency on January 4, 1999) as well as the Propofol that was tentatively approved under ANDA Please provide the FDA rationale for applying this additional, new requirement to this specific ANDA, since precedent has already been set under two previous ANDAs of the acceptability of the upper stability limit of 22°C by the Agency.

Secondly, the Agency requested stability data at the lower end of the storage condition, i.e., 4°C. In response, Gensia Sicor did not perform a stability study at the lower storage temperature condition, therefore no data are available.

As for the third point, the Agency requested data from a freeze-thaw study. Gensia Sicor did not perform a freeze-thaw study and therefore no data are available. Our rationale for excluding a freeze-thaw study from our evaluation of the product is as follows:

1) The labeling of the reference listed drug and labeling of Gensia Sicor's product, specifically states, "Do not freeze." Gensia Sicor consciously matched the current labeled storage condition for the generic with that of the reference listed drug, based upon our confidence in the innovator's experience regarding stability. Since the labeling of both products indicates the product will be compromised if frozen, we question FDA's rationale that data be provided to support a negative claim.

2) In addition, we wish to reiterate that freeze-thaw studies were not a requirement for approval and tentative approval of ANDA 75-102 and ANDA respectively. We would like to understand FDA's rationale for applying this additional, new requirement to this specific ANDA, since precedent has already been set with the aforementioned approved ANDAs.

3) Finally, Gensia Sicor did not include a freeze-thaw study because it is generally viewed that emulsions should not be frozen and is known to compromise the integrity of an emulsion. This characteristic of an emulsion is well documented in the literature (for an example an excerpt of the literature is provided in **Attachment 2**, Advances in Clinical Nutrition. *British Library Cataloguing in Publication Data*. 1983). According to the cited reference, conventional fat emulsions can be destabilized by freeze/thaw cycles comprising of rapid deep freeze followed by thawing at room temperature. Gensia Sicor did not incorporate a freeze-thaw cycle into the current stability program because the data, i.e., a broken emulsion, would have no inherent value in assessing the quality of the product.

The final point requested by the Agency related to a commitment to perform commercial stability in accordance with the upper temperatures stated in either the FDA stability guidance or the ICH stability guideline, as well as at the lower temperature of 4°C. In response to this request, we wish to reiterate that the temperature range established for Gensia Sicor's Propofol product corresponds with the labeled storage conditions of the reference listed drug, Diprivan. Our current convention is to monitor product stability at the upper stability temperature, which provides the greatest stress on the product. We also note that neither FDA nor ICH stability guidance specify that stability be performed at the lower limit of a stated storage condition. We are not aware that a new requirement is in place to evaluate the lower end of the storage conditions. Again, a commitment to perform commercial stability at the upper temperature defined per the stability guidances, as well as at the lower temperature of 4°C were not a requirement for approval and tentative approval of ANDA 75-102 and ANDA , respectively. We would like to understand FDA's rationale for applying this additional, new requirement to this specific ANDA, since precedent has already been set with the aforementioned approved ANDAs.

Therefore, Gensia Sicor elects to retain the storage stability range of 4-22°C as indicated on the labeling and will provide stability data from the stability program as currently committed to in the ANDA. Since, the proposed stability program for Propofol in prefilled syringes is identical to the program presented in our two approved ANDAs for Propofol and duplicates the storage conditions stated in the labeling of the reference listed drug, AstraZeneca's Diprivan, our position is well supported.

In closing, we are aware that Dr. Sayeed indicated that he would investigate the stability conditions maintained in the NDA for AstraZeneca's Diprivan. Although, we are aware that this information cannot be publicly disclosed, we hope that his investigation will shed additional light on the use of a non-standard temperature range to define the storage conditions of this unique, emulsion product.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808. I may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

H:\DATA\IRG\PRO75392\AMENDS\Amend10.doc

cc: Acting District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

GensiaSicor™
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November 12, 1999

NDA 075392 AMENDMENT
AF

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL
ANDA 75-392

LABELING AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Reference is also made to our amendment dated August 30, 1999. Further reference is made to the Agency's facsimile dated October 13, 1999.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the labeling changes as requested. Twelve (12) samples of the final printed package insert are provided in **Attachment 1**. A side-by-side comparison of our proposed package insert along with our last submission is provided in **Attachment 2** for your review with all differences annotated and explained.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808. I may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

H:\DATA\IRG\PRO75392\AMENDS\Amend7.doc

cc: Mr. Thomas Sawyer
Acting District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

NOV 15 1999

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
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August 30, 1999

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA DRUG AMENDMENT
AF

RE: Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe ANDA 75-392

LABELING AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Reference is also made to our amendments dated December 22, 1998 and May 7, 1999. Further reference is made to the Agency's facsimile dated July 15, 1999.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the labeling changes as requested. Twelve (12) samples of the final printed package insert are provided in **Attachment 1**. A side-by-side comparison of our proposed package insert along with our last submission is provided in **Attachment 2** for your review with all differences annotated and explained.

In response to deficiency items #3a(i), Gensia Sicor prefers not to combine the package insert text from ANDA 75-102 and ANDA 75-392, as the labeling for the vial configuration. For marketing reasons, Gensia Sicor proposes to have the package insert to ANDA 75-102 remain specific and dedicated to the 20 mL, 50 mL, and 100 mL vials only. The combined information will be reflected in the labeling of the 20 mL prefilled syringe only. In the event Gensia Sicor decides to combine the labeling text for the vial configuration under ANDA 75-102, we will provide notification pursuant to 21 CFR 314.70 (c), under a "Supplement - Changes Being Effected."

RECEIVED
AUG 31 1999

Gensia Sicor Pharmaceuticals, Inc. • 17 Hughes • Irvine CA • 92618-1902 • USA
Phone (714) 455-4700, (800) 729-9991 • Fax (714) 855-8210 • http://www.gensiasicor.com

In response to deficiency item #3a(ii), due to a difference in the filling lines used to produce the Propofol product in vials versus in syringe, the processes achieve slightly different ranges of pH. Therefore, different ranges have been established for the two different configurations, i.e., pH range of 4.5 - 6.4 for the vials and pH range of 4.5 - 6.6 for the syringe. Hence, Gensia Sicor proposes to define a pH specification of 4.5 – 6.6 in the "Description" section of the package insert under ANDA 75-392. This broader pH range encompasses the pH range established for the vial configurations, that will be reflected in the "How Supplied" section of the package insert under this ANDA. Please note that the pH release specifications of 4.5 – 6.4 as specified under ANDA 75-102 have not changed and remain the final release specifications as established in the approved ANDA 75-102.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Elvin O. Gustafson

for Rosalie A. Lowe
Associate Director, Regulatory Affairs

H:\DATA\IRG\PRO75392\AMENDS\Amend7.doc

cc: Mr. Thomas Sawyer
Acting District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

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August 18, 1999

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

RE: Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe ANDA 75-392

SPECIAL LETTER OF CORRESPONDENCE

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Reference is also made to the telephone call on August 18, 1999 from Mr. Glen Smith, Team Leader, OGD, regarding the source of the Egg Yolk Phospholipid used in the manufacture of Propofol Injectable Emulsion.

Pursuant to Mr. Smith's request, attached is a letter of declaration to confirm that Gensia Sicor sources Egg Yolk Phospholipid, that is used in the manufacture of the generic Propofol, exclusively from

If there are any questions concerning this correspondence, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

\\GS01\DOS\DATA\RG\PRO75392\CORRESPD\Special8-18-99.doc

cc: Mr. Thomas Sawyer
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 19 1999
OGD

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
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FPL
ORIG AMENDMENT
AF

May 7, 1999

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL
(with 0.025% Sodium Metabisulfite)
Prefilled Syringe
ANDA 75-392

LABELING AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Reference is also made to our amendment dated December 22, 1998. Further reference is made to the Agency's facsimile dated April 6, 1999.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the labeling changes as requested. Twelve (12) samples of the final printed labeling (container, carton, and package insert) are provided in **Attachment 1**. A side-by-side comparison of our proposed labeling along with our last submission is provided in **Attachment 2** for your review with all differences annotated and explained.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

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RECEIVED
MAY 10 1999
GENERIC DRUGS

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

GensiaSicor™
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December 22, 1998

NDA ORIG AMENDMENT
N/AF

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe
ANDA 75-392

AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Reference is also made to the Agency's facsimile dated December 11, 1998.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the labeling changes as requested.

Furthermore, Gensia Sicor has received additional labeling changes for Propofol Injectable Emulsion supplied in vials (ANDA 75-102). These changes impact the labeling for Propofol Injectable Emulsion supplied in syringes. Therefore, in accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, Gensia Sicor Pharmaceuticals, Inc., hereby commits to incorporate the requisite labeling revisions to the syringe labeling as specified in the Agency's facsimile dated December 21, 1998 under ANDA 75-102. We further commit to assuring that the revisions requested by FDA will be reflected in the labeling utilized for the commercial launch of this product.

DEC 23 1998

GENERIC DRUGS

GensiaSicor Pharmaceuticals • 17 Hughes • Irvine CA • 92618-1902 • USA
Phone (714) 455-4700, (800) 729-9991 • Fax (714) 855-8210 • http://www.gensiasicor.com

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PRO75392\AMENDS\AMEND5.WPD

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

GensiaSicor™
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NEW CORRESP
NC

December 1, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe ANDA 75-392

PATENT AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Further reference is made to the amendment dated July 30, 1998, which provided documentation of receipt on July 17, 1998, and July 13, 1998, for our Notice of Certification by Zeneca Ltd and Zeneca Inc., respectively.

In accordance with the provisions of Section 314.107(f)(2) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to inform the Agency of the legal actions related to this application.

We wish to inform the Agency that neither Gensia Sicor nor its legal representatives have been served with a legal complaint, that has been precipitated by our Notice of Certification received by Zeneca Ltd or Zeneca Inc. To the best of our knowledge, we are not aware of any legal action taken within the requisite 45 days, that expired on August 31, 1998, by Zeneca or its legal representatives.

RECEIVED
DEC 0 2 1998
GENERIC DRUGS

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

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NEW CORRESP

uly 30, 1998

r. Douglas Sporn
ffice of Generic Drugs
enter for Drug Evaluation and Research
ood and Drug Administration
letro Park North II, HFD-600
ttention: Documentation Control Room 150
500 Standish Place,
ockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe ANDA 75-392

AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Further reference is made to the Notice of Certification amendment dated July 8, 1998.

In accordance with the provisions of Section 314.95(e) of the Code of Federal Regulations, Title 21, we hereby amend this application to document receipt of the notice required under paragraph (a) of Section 314.95 by each person provided the notice. Copies of the return receipts are attached.

We trust that the information provided in this amendment is satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-2808 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PRO75392\AMENDS\AMEND3.WPD
cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

RECEIVED
JUL 31 1998
GENERIC DRUGS

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GensiaSicor™
PHARMACEUTICALS
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NDA 75-392

NC

July 8, 1998

RECEIVED
JUL 09 1998
GENERIC DRUGS

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place,
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe
ANDA 75-392

AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998.

In accordance with Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.95(b), we hereby amend this application to include this certification that the notice has been provided to Zeneca Ltd., UK, and Zeneca Inc., USA, the holders of the approved application for Diprivan® and the owners of the U.S. Patent Nos. 5714520, 5731355, and 5731356, at the same time this amendment was submitted to the application. The notice met the content requirements of 21 CFR 314.95(c) and was sent by certified/registered mail, return receipt requested.

GensiaSicor Pharmaceuticals • 17 Hughes • Irvine CA • 92618-1902 • USA
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We trust that the information provided in this amendment satisfactory for your review and approval. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-2808 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PRO75392\AMENDS\AMEND2.WPD

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

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ORIG AMENDMENT

AA

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JUN 25 1998

GENERIC DRUGS

June 24, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place,
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe ANDA 75-392

FACSIMILE AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's ANDA 75-392 for Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe, which was submitted to the Agency on May 29, 1998. Reference is also made to the request from Lt. Nasser Mahmud, Regulatory Project Manager, Office of Generic Drugs to revise the proposed maximum batch size designated in this application.

Specifically, FDA has determined that the exhibit bulk size, which is the basis for the 10% rule calculation, is liters for this application; and not liters as indicated in our original submission. Therefore, the maximum commercial batch size allowed for the Propofol Injectable Emulsion with Sodium Metabisulfite, 20 mL syringes, will be liters. To reflect this revised maximum batch size, we are providing a revised narrative of the Blank Master Production and Control (Batch) Records (refer to **Attachment 1**) and the revised compounding document, page 6 of 6, step 48 (refer to **Attachment 2**).

In addition, we have revised page 200527 of the ANDA to correct a typographical error. The lot number of the finished dosage form to be retained for FDA testing is XP7N314F1 (refer to **Attachment 3**).

Nadine 7-6-98

We trust that the information provided is in accordance with the request from the Agency. Should you have any additional questions regarding our application, please feel free to contact me at (949) 457-2808.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PRO75392\AMENDS\AMEND1.WPD
Attachments (3)

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

GensiaSicor™
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May 29, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place,
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite) Prefilled Syringe
ANDA: Number to be Assigned

Dear Mr. Sporn:

In accordance with Section 314.92 of the *Code of Federal Regulations, Title 21*, we hereby submit an Abbreviated New Drug Application for Propofol Injectable Emulsion (with 0.025% Sodium Metabisulfite), a parenteral emulsion preparation supplied as:

Strength	Drug Content	How Supplied
10 mg/mL	200 mg Propofol Injectable Emulsion/syringe	200 mg in a 20 mL syringe

Propofol Injectable Emulsion, 10 mg/mL (with 0.025% Sodium Metabisulfite), is the generic version of Diprivan® (Propofol Injectable Emulsion) which is currently manufactured by Zeneca, Ltd. Zeneca's drug product appears in the FDA listing titled *Approved Drug Products with Therapeutic Equivalence Evaluation, 17th Edition.* Our drug product has the same active ingredients, dosage form, strength, route of administration, and conditions of use as Zeneca's listed drug product. Furthermore, Gensia Sicor's drug product contains the same inactive ingredients except for the preservative, Gensia Sicor has elected to substitute with 0.025% Sodium Metabisulfite in accordance with 21 CFR Part 314.94 (a) (9) (iii).

Four (4) copies of the proposed labeling have also been provided in **Section V** of the application in both the archival and review copies.

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The application consists of three (3) volumes and has been formatted in accordance with the Office of Generic Drug's Policy and Procedure Guide #30-91 issued April 10, 1991; and, as modified by FDA's October 14, 1994 letter to all NDA, ANDA, and AADA applicants. Copies are provided as follows:

1) One (1) Archival Copy bound in Blue Jackets
2) One (1) Review Copy bound in Red Jackets

A true copy of this application, which was bound in Burgundy Jackets, has been submitted to the U.S. Food and Drug Administration of Irvine, California, Los Angeles District Office.

Since the product which is the subject of this application is non-compendial, three (3) additional methods validation packages have been included and are marked "Analytical Methods." These three additional copies are identical to **Section XVI** as presented in the archival and review copies, and have been separately bound in Black Jackets.

In addition, provided in **Section I** is a Methods Testing Commitment.

We trust you will find the information in this application satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting me at (949) 457-2808 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PROPSMBS\ANDA\SEC1.

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715