CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75392

ADMINISTRATIVE DOCUMENTS

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-392** Date of Submission: **November 12, 1999**

Applicant's Name: **Gensia Laboratories, Ltd.**

Established Name: **Propofol Injectable Emulsion 1% (10 mg/mL)**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS: 20 mL prefilled syringe

Satisfactory in FPL as of 5/7/99 submission

CARTON LABELING: 20 mL prefilled syringe

Satisfactory in FPL as of 5/7/99 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 11/12/99 submission

REVISIONS NEEDED POST-APPROVAL:

None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diprivan ® (NDA 19-627)

NDA Number: NDA 19-627

NDA Drug Name: Diprivan®

NDA Firm: Zeneca LTD.

Date of Approval of NDA Insert and supplement #:April 29, 1999 (S-031)

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Diprivan®

Basis of Approval for the Carton Labeling: Diprivan®

Other Comments:

RLD contains EDTA as a preservative whereas the sponsor's product uses sodium metabisulfite.

FOR THE RECORD

1. MODEL LABELING – Both insert labeling from NDA 19-627/S-031 approved 4/29/99 & ANDA 75-102/S-003, approved 5/14/99.

2. The firm was previously asked to delete the statement '
from the container and carton respectively because it was revealed in the Acknowledge and Retain letter dated December 23, 1997, for NDA 19-627/S-027 that '

3. INACTIVE INGREDIENTS - See page 100070 Section VII, Volume 1.1. Note RLD cites "glycerin". Gensia cites "Glycerol" on the labels and labeling but Glycerin in the Components/Composition section. Glycerin USP monograph lists glycerol as an alternate name and this is acceptable. Also, Gensia chooses to refer to "Egg Lecithin" as "Egg yolk phospholipid". The chemist was consulted and finds this acceptable.

4. It should be noted that the pH range is listed as 4.5 - 6.4 for ANDA 75-102 however, the pH range listed for the combined insert labeling submitted under ANDA 75-392 is 4.5 – 6.6. There are no chemistry supplements that provide for this change under ANDA 75-102 and also no supplements that provide for a combined insert labeling. This issue was brought to the Chemist's attention (Raymond Brown) on October 12, 1999. The firm explains that the slight differences in the filling lines used for the vials and syringes result in a slightly inconsistent pH. The consulted chemist believes that the pH difference is insignificant and finds this acceptable.

5. PATENTS/EXCLUSIVITIES

   Patent 4056635 expired 11-1-96.
   Patent 4798846 expired on 3-19-97.

   Patent 5714520 expires on March 22, 2015. Gensia states that this patent □will not be infringed upon by the manufacture, use, or sale by Gensia Sicor Pharmaceuticals, Inc., for which this amendment is submitted.□ Paragraph IV Certification cited.

   Patent 5731355 provides for method of producing analgesia **expires March 22, 2015. Paragraph IV Certification cited.**

   Patent 5731356 provides for a method for limiting the potential for microbial growth **expires March 22, 2015. Paragraph IV Certification cited.**

   Exclusivities, I-99, for Pediatric Anesthesia in Children 3 years and older expired on 10-26-96.
   Exclusivity, I-90, for Intensive Care Unit Sedation expired on 3-8-96.

   Exclusivity, NP, for new product containing **expired on June 11, 1999.** Gensia states that they are "not seeking marketing approval for an

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   Not USP.

   RLD "Store between 4° – 22°C (40° – 72°F). DO NOT FREEZE."

ANDA "Store between 4° – 22°C (40° – 72°F). DO NOT FREEZE."

7. Gensia is the sole manufacturer of the drug product. See pp 335, 354 of original submission.

8. BIOEQUIVALENCE - Completed

9. PACKAGING CONFIGURATION

RLD: 20 mL ampuls, 50 mL and 100 mL infusion vials, and 20 mL and 50 mL pre-filled syringes.

ANDA: 20 mL single dose prefilled syringe.

Earlier RLD labeling stated "Protect from light." However, newer labels do not have this statement. Also, in a previous review for another ANDA, the comment was made in the FTR that if packaged with nitrogen, the statement was not required.

10. The RLD has one revision in the box of warnings - has been revised to read "Supports microbial growth". has been deleted since the addition of retards microbial growth. It is noted that this is not an antimicrobially preserved product under USP standards. To date, we have not received FPL for the supplement approved on 6-11-96.

11. The firm has proposed a combined insert labeling which includes labeling for the approved ANDA 75-102 (vials). However, the sponsor wants the labeling for 75-102 remain to be specific for the vials only. We find this acceptable.

Date of Review: November 23, 1999 Date of Submission: November 12, 1999

Primary Reviewer: Chan Park /S/ 11/30/99

Team Leader: Charles V. Hoppes

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cc: ANDA 75-392
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
V:\FIRMSAM\GENSIA\LTRS&REV\75392.apl
REVIEW

/S/ 11/30/99 Concur. Jean 11/30/1999

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-392** Date of Submission: **August 30, 1999**

Applicant's Name: **Gensia Laboratories, Ltd.**

Established Name: **Propofol Injectable Emulsion 1% (10 mg/mL)**

Labeling Deficiencies:

INSERT – Due to the recent approved revision of the insert labeling for the reference listed drug, Diprivan® Injectable Emulsion, we ask that you revise your insert labeling as follows:

PRECAUTIONS

i. General - Include the following text in bold face type as the eleventh paragraph.

... is unknown.

Very rarely, cases of unexplained postoperative pancreatitis (requiring hospital admission) have been reported after anesthesia in which propofol was one of the induction agents used. Due to a variety of confounding factors in these cases, including concomitant medications, a causal relationship to propofol is unclear.

Propofol has no ...

ii. Include the following subsection as the last one under this section.

Geriatric Use: The effect of age on induction dose requirements for propofol was assessed in an open study involving 211 unpremedicated patients with approximately 30 patients in each decade between the ages of 16 and 80. The average dose to induce anesthesia was calculated for patients up to 54 years of age and for patients 55 years of age or older. The average dose to induce anesthesia in patients up to 54 years of age was 1.99 mg/kg and in patients above 54 it was 1.66 mg/kg. Subsequent clinical studies have demonstrated lower dosing requirements for subjects greater than 60 years of age.

Please revise your package insert labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes.

www.fda.gov/cder/ogd/rld/labeling review branch

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-392** Date of Submission: **May 7, 1999**

Applicant's Name: **Gensia Laboratories, Ltd.**

Established Name: **Propofol Injectable Emulsion 1% (10 mg/mL)**

Labeling Deficiencies:

1. CONTAINER - 20 mL prefilled syringe

   Satisfactory in FPL in the May 7, 1999, submission.

2. CARTON - 20 mL prefilled syringe

   Satisfactory in FPL in the May 7, 1999, submission.

3. INSERT

   a. GENERAL

      i. We note that you have submitted a combined insert labeling which includes labeling for your approved ANDA 75-102. Please submit a labeling supplement to that application to provide for a combined insert labeling.

      ii. The pH range for the vials under ANDA 75-102 is and the pH range for this application is We are not aware of any chemistry supplements for ANDA 75-102 that provides for a change in the pH range. Please revise and/or explain.

   b. DOSAGE AND ADMINISTRATION

      i. Guidelines for Aseptic Technique for General Anesthesia/MAC Sedation

         Revise the last sentence of the first paragraph to read: "...within 6 hours after the vials or prefilled syringes have..."

ii. Guidelines for Aseptic Technique for ICU Sedation

(a) Revise the second sentence to read: "…directly from the vial/prefilled syringe, strict…"

(b) Delete the third sentence from the first paragraph.

Please revise your labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes.

www.fda.gov/cder/ogd/rld/labeling_review_branch

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, *Warning Statements that might be in red* for the NDA)	X		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD

1. MODEL LABELING - Both insert labeling from NDA 19-627/S-027 approved 6/11/96, & ANDA 75-102/S-003, approved 5/14/99.

2. The firm was previously asked to delete the statement

from the container and carton respectively

because it was revealed in the Acknowledge and Retain letter dated December 23, 1997, for NDA 19-627/S-027 that

3. INACTIVE INGREDIENTS - See page 100070 Section VII, Volume 1.1. Note RLD cites "glycerin". Gensia cites "Glycerol" on the labels and labeling but Glycerin in the Components/Composition section. Glycerin USP monograph lists glycerol as an alternate name and this is acceptable. Also, Gensia chooses to refer to "Egg Lecithin" as "Egg yolk phospholipid". The chemist was consulted and finds this acceptable.

4. It should be noted that the pH range is listed as for ANDA 75-102 however, the pH range listed for the combined insert labeling submitted under ANDA 75-392 is As of June 30, 1999, there are no chemistry supplements that provide for this change under ANDA 75-102 and also no supplements that provide for a combined insert labeling.

5. PATENTS/EXCLUSIVITIES

Patent 4056635 expired 11-1-96.
Patent 4798846 expired on 3-19-97.

Patent 5714520 expires on March 22, 2015. Gensia states that this patent "will not be infringed upon by the manufacture, use, or sale by Gensia Sicor Pharmaceuticals, Inc., for which this amendment is submitted." Paragraph IV Certification cited.

Patent 5731355 provides for method of producing analgesia **expires March 22, 2015. Paragraph IV Certification cited.**

Patent 5731356 provides for a method for limiting the potential for microbial growth **expires March 22, 2015. Paragraph IV Certification cited.**

Exclusivities, I-99, for Pediatric Anesthesia in Children 3 years and older expired on 10-26-96.
Exclusivity, I-90, for Intensive Care Unit Sedation expired on 3-8-96.

Exclusivity, NP, for new product containing **expired on June 11, 1999.** Gensia states that they are

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
Not USP.

RLD "Store between 4° - 22°C (40° - 72°F). DO NOT FREEZE."

ANDA "Store between 4° - 22°C (40° - 72°F). DO NOT FREEZE."

7. Gensia is the sole manufacturer of the drug product. See pp 335, 354 of original submission.

8. BIOEQUIVALENCE - Completed

9. PACKAGING CONFIGURATION

RLD: 20 mL ampuls, 50 mL and 100 mL infusion vials, and 20 mL and 50 mL pre-filled syringes.

ANDA: 20 mL single dose prefilled syringe.

Earlier RLD labeling stated "Protect from light." However, newer labels do not have this statement. Also, in a previous review for another ANDA, the comment was made in the FTR that if packaged with nitrogen, the statement was not required.

10. The RLD has one revision in the box of warnings - has been revised to read "Supports microbial growth". has been deleted since the addition of retards microbial growth. It is noted that this is not an antimicrobially preserved product under USP standards. To date, we have not received FPL for the supplement approved on 6-11-96.

Date of Review: June 30, 1999 Date of Submission: May 7, 1999

Primary Reviewer: Koung Lee /S/ 7/2/99

Team Leader: Charles V. Hoppes /S/ 7/2/99

7/12/1999

cc: ANDA 75-392 Comm: /S/
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
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REVIEW

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-392** Date of Submission: **December 22, 1998**

Applicant's Name: **Gensia Laboratories, Ltd.**

Established Name: **Propofol Injectable Emulsion 1% (10 mg/mL)**

Labeling Deficiencies:

1. CONTAINER - 20 mL prefilled syringe

   a. Relocate "Contains a Sulfite" between "200 mg/20 mL propofol" and "10 mg/mL" and revise it to appear with the same prominence as "200 mg/20 mL propofol" on the principal display panel.

   b. Delete `

   c. We encourage you to relocate the "R_x only" to the principal display panel.

2. CARTON - 20 mL prefilled syringe

   a. See comment a. under CONTAINER. This revision should also be made for the expression of strength on the side and top panels.

   b. Delete

   c. Revise the last sentence to read "Patients should be continuously monitored, and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available."

3. INSERT

   a. TITLE

      We encourage you to relocate "R_x only" to this section.

b. PRECAUTIONS

i. General

Replace the semicolon with a comma in the third sentence.

ii. Pharmacokinetics

Place a comma between "…constant over time" and "but decreases as…" in the first sentence of the fourth paragraph.

iii. Pediatric Anesthesia (Initiation of MAC Sedation)

Replace the semicolon with a comma between "…be adequately sedated" and "and the peak…" in the last sentence of the first paragraph.

c. WARNINGS

i. Replace the semicolon with a comma between "…be continuously monitored" and "and facilities for…" in the second sentence of the first paragraph.

ii. Add the sulfite warning statement per 21 CFR 201.22.

d. PRECAUTIONS

i. General

Delete

from the fifth paragraph.

ii. The second subsection should be presented as follows:

Intensive Care Unit Sedation: (See WARNINGS and DOSAGE AND ADMINISTRATION, Handling Procedures.)

iii. Drug Interactions

Please revise "…and fentanyl, etc). and…" with "…and fentanyl, etc.) and…" and "…chloral hydrate, droperidol, etc).. These agents…" with "…chloral hydrate, droperidol, etc.). These agents…"

iv. Labor and Delivery

Please replace the semicolon with a comma in the second sentence.

d. DOSAGE AND ADMINISTRATION

i. Dilution Prior to Administration

Delete the first sentence and revise the second sentence to read as "When propofol injectable emulsion is diluted prior to administration, it should only be diluted with 5% dextrose injection, and it…"

ii. Administration with Other Fluids

Add "Lactated Ringers Injection" as the second bullet.

e. HOW SUPPLIED

Since this insert is specific to the syringe, we request that you relocate the information for the vials to appear under the heading "Also available as:". Alternatively, you may revise to make a combined insert, provided the text "Single Dose Syringe" is deleted from the insert title (two places) and the following text is added as the third sentence in the "Guidelines for Aseptic Technique for ICU Sedation" subsection of the DOSAGE AND ADMINISTRATION section "The syringe(s) should be labeled with appropriate information including the date and time the vial was opened.

Please revise your labels and labeling, as instructed above, and submit final printed container labels and carton labeling, and final print insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, *Warning Statements that might be in red* for the NDA)	X		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD

1. MODEL LABELING - NDA 19-627 Diprivan® Injectable Emulsion 1%; Zeneca LTD: Approved 4-21-95 labeling issues, and 6-11-96 Supplement - Formulation Revision (SCF-027) approved labeling, revised 5-96.

2. The firm is asked to delete the statement from the container and carton respectively. It was revealed in the Acknowledge and Retain letter dated December 23, 1997, for NDA 19-627/S-027 that

3. INACTIVE INGREDIENTS - See page 100070 Section VII, Volume 1.1. Note RLD cites "glycerin". Gensia cites "Glycerol" on the labels and labeling but Glycerin in the Components/Composition section. Glycerin USP monograph lists glycerol as an alternate name and this is acceptable. Also, Gensia chooses to refer to "Egg Lecithin" as "Egg yolk phospholipid". The chemist was consulted and finds this acceptable. It should be noted that the pH is now listed as 4.5 - 6.4 compared to 7 to 8.5. The pH difference was found to be acceptable by Dr. Mary Fanning.

4. PATENTS/EXCLUSIVITIES

Confirmed through Orange Book Cumulative Supplement 6 Jan'98-Jun'98.

Patent 4056635 expired 11-1-96.

Patent 4798846 expired on 3-19-97.

Patent 5714520 expires on March 22, 2015. Gensia states that this patent "will not be infringed upon by the manufacture, use, or sale by Gensia Sicor Pharmaceuticals, Inc., for which this amendment is submitted." Paragraph IV Certification cited.

Patent 5731355 provides for method of producing analgesia **expires March 22, 2015. Paragraph IV Certification cited.**

Patent 5731356 provides for a method for limiting the potential for microbial growth **expires March 22, 2015. Paragraph IV Certification cited.**

Exclusivities, I-99, for Pediatric Anesthesia in Children 3 years and older expired on 10-26-96.

Exclusivity, I-90, for Intensive Care Unit Sedation expired on 3-8-96.

Exclusivity, NP, for new product containing **expires on June 11, 1999.** According to the information listed in the 18TH edition of the Approved Drug Products, Zeneca Ltd., has been granted a period of marketing exclusivity for

Diprivan®. The exclusivity granted will expire on June 11, 1999. Indication: New Product. Gensia states that they are "not seeking marketing approval for an EDTA-preserved (Propofol) Injectable Emulsion, 10 mg/mL product."

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
Not USP. Both ANDA and RLD: Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended.

The RLD storage recommendation has been revised to read "Store between 4° - 22°C (40° - 72°F). DO NOT FREEZE."

6. Gensia is the sole manufacturer of the drug product. See pp 335, 354 of original submission.

7. BIOEQUIVALENCE - Completed

8. PACKAGING CONFIGURATION

RLD: 20 mL ampuls, 50 mL and 100 mL infusion vials, and 20 mL and 50 mL pre-filled syringes.

ANDA: 20 mL single dose prefilled syringe.

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Date of Review: April 5, 1999 Dates of Submission: **December 22, 1998**

Primary Reviewer: Koung Lee /S/ 4/5/99

Team Leader: Charles V. Hoppes /S/

4/6/99

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-392** Date of Submission: **May 29, 1998**

Applicant's Name: **Gensia Laboratories, Ltd.**

Established Name: **Propofol Injectable Emulsion 1% (10 mg/mL)**

Labeling Deficiencies:

1. CONTAINER - 20 mL prefilled syringe

   a. Bold and capitalize "sodium metabisulfite" in your listing of ingredients.

   b. Because of the potential for allergic-type reaction to sodium metabisulfite and because the reference listed drug, Diprivan, does not contain this inactive ingredient, please add "Contains a Sulfite" with the same prominence as the total volume expression on the principal display panel.

   c. Please replace with "• CONTAINS A SULFITE; microbial growth may still be supported."

2. CARTON - 20 mL, 50 mL, and 100 mL

   a. See comments under CONTAINER.

   b. Please relocate "R_x *only*" to the principal display panel.

3. INSERT

   a. TITLE

      Please add "Contains a Sulfite".

   b. PRECAUTIONS (General)

      The 11th paragraph "Very rarely, cases...to propofol is unclear." should be deleted.

c. DOSAGE AND ADMINISTRATION (Administration with Other Fluids:)

i. On line 10 in the fifth paragraph of Administration with Other Fluids subsection - **SEDATION (SEE Clinical Trials...**

ii. Delete in the second sentence under Dilution Prior to Administration subsection.

iii. Insert "Propofol injectable emulsion should be prepared for single patient use only." as the first sentence under Guidelines for Aseptic Technique for ICU Sedation subsection.

Please revise your labels and labeling, as instructed above, and submit final printed container labels and carton labeling, and final print (or draft, if you prefer) insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Bob L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, *Warning Statements that might be in red* for the NDA)	X		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD

1. MODEL LABELING - NDA 19-627 Diprivan® Injectable Emulsion 1%; Zeneca LTD: Approved 4-21-95 labeling issues, and 6-11-96 Supplement - Formulation Revision (SCF-027) approved labeling, revised 5-96.

2. This is a potential first generic.

3. INACTIVE INGREDIENTS - See page 100070 Section VII, Volume 1.1. Note RLD cites "glycerin". Gensia cites "Glycerol" on the labels and labeling but Glycerin in the Components/Composition section. Glycerin USP monograph lists glycerol as an alternate name and this is acceptable. Also, Gensia chooses to refer to "Egg Lecithin" as "Egg yolk phospholipid". The chemist was consulted and finds this acceptable. It should be noted that the pH is now listed as 4.5 - 6.4 compared to 7 to 8.5. The pH difference was found to be acceptable by Dr. Mary Fanning.

4. PATENTS/EXCLUSIVITIES

Confirmed through Orange Book Cumulative Supplement 6 Jan'98-Jun'98.

Patent 4056635 expired 11-1-96.

Patent 4798846 expired on 3-19-97.

Patent 5714520 expires on March 22, 2015. Gensia states that this patent "will not be infringed upon by the manufacture, use, or sale by Gensia Sicor Pharmaceuticals, Inc., for which this amendment is submitted." Paragraph IV Certification cited.

Patent 5731355 provides for method of producing analgesia **expires March 22, 2015. Paragraph IV Certification cited.**

Patent 5731356 provides for a method for limiting the potential for microbial growth **expires March 22, 2015. Paragraph IV Certification cited.**

Exclusivities, I-99, for Pediatric Anesthesia in Children 3 years and older expired on 10-26-96.

Exclusivity, I-90, for Intensive Care Unit Sedation expired on 3-8-96.

Exclusivity, NP, for new product containing **expires on June 11, 1999.** According to the information listed in the 18TH edition of the Approved Drug Products, Zeneca Ltd., has been granted a period of marketing exclusivity for Diprivan®. The exclusivity granted will expire on June 11, 1999. Indication: New Product. Gensia states that they are

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
Not USP. Both ANDA and RLD: Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended.

The RLD storage recommendation has been revised to read "Store between 4° - 22°C (40° - 72°F). DO NOT FREEZE."

6. Gensia is the sole manufacturer of the drug product. See pp 335, 354 of original submission.

7. BIOEQUIVALENCE - Completed

8. PACKAGING CONFIGURATION
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Date of Review: **November 25, 1998** Dates of Submission: **May 29, 1998**

Primary Reviewer: Koung Lee 12/10/98

Team Leader: Charles V. Hoppes /S/ 12/11/98

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cc: ANDA 75-392
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
X:\NEW\FIRMSAM\GENSIA\LTRS&REV\75392NA1.Label
REVIEW

RECORD OF TELEPHONE CONVERSATION

DATE: June 18, 1998

DRUG PRODUCT: Propofol Injectable Emulsion

ANDA NUMBER: 75-392

COMPANY: Gensia Sicor

NAME OF COMPANY REPRESENTATIVE(S): Rosalie Lowe

NAME OF OGD REPRESENTATIVE(S): Nasser Mahmud

Telecon initiated by: Nasser Mahmud

COMPANY TELEPHONE: 949-457-2808

I called Rosalie to request clarification of size of executed batch. It appears that the size of the executed batch is liters but the scale up production batch is liters. Rosalie said that the executed batch is liters but this information is not clear in the ANDA.
She called back and said that on page 100248 (vol. 1) the information shows that Kg Liters) were dedicated to the ANDA. I told her that based on this information, the production batch could be no larger than Liters.
This information was repeated again with Elvia Gustavson of Gensia Sicor on June 19, 1998. Elvia committed to sending revised master production batch records to indicate a liter batch.