

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 22-156**

**CHEMISTRY REVIEW(S)**

**Cleviprex**  
**(clevidipine butyrate)**  
**Injectable Emulsion**

**NDA 22-156**

**Division Director Review**  
**Chemistry, Manufacturing, and Controls**

**Applicant:** The Medicines Company  
8 Campus Drive  
Parsippany, NJ 07054

**Indication:** \_\_\_\_\_

**Presentation:** Cleviprex Injectable Emulsion is supplied as a single strength, sterile, oil-in-water emulsion of 0.5 mg/mL of clevidipine butyrate in 50 mL or 100 mL clear glass bottles, both fitted with black rubber stoppers with an aluminum overseal.

**EER Status:** Acceptable 03-AUG-2007

**Consults:** EA – Categorical exclusion granted 21 CFR §25.31(b)  
Microbiology - Approved 17-JUL-2008  
Methods Validation – Revalidation by Agency not necessary.

**Original Submission:** 02-JUL-2007

**Post-Approval Agreements:** None

**Drug Substance:**

The drug substance, clevidipine butyrate, is a small, synthetic, New Molecular Entity (NME) with an empirical formula of  $C_{21}H_{23}Cl_2NO_6$  a molecular weight of 456.3. Known chemically as 4-(2',3'-Dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid, 3-butyryloxymethyl ester 5-methyl ester. it is manufactured as a racemic mixture of (+)-S and (-)-R enantiomers. The drug substance is a \_\_\_\_\_, practically insoluble in water, \_\_\_\_\_

\_\_\_\_\_

The chemistry, manufacturing, and controls information for the drug substance is appropriately referenced, is described in \_\_\_\_\_ type II DMF \_\_\_\_\_ has been reviewed, and is concluded to be adequate.

The structure of clevidipine butyrate was elucidated by infrared (IR) spectrophotometry, proton and carbon (<sup>1</sup>H and <sup>13</sup>C) nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry, and elemental analysis. The results of the analytical studies as well as information on the enantiomers and polymorphs were referenced to DMF \_\_\_\_\_ from a routine production lot and information is available in DMF \_\_\_\_\_

The proposed release specification for clevidipine butyrate includes

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Adequate stability data were provided to support a retest date of \_\_\_\_\_ for bulk drug substance, packed in \_\_\_\_\_ bags inside \_\_\_\_\_ containers, stored at controlled room temperature, 20°-25°C (68°-77°F), with excursions from 15°C to 30°C, protected from light.

**Conclusion:** Drug substance is acceptable.

**Drug Product:**

Cleviprex is supplied as a single-use, sterile, oil-in-water emulsion either in 50 mL \_\_\_\_\_ or 100 mL \_\_\_\_\_ clear glass bottles, both fitted with black \_\_\_\_\_ rubber stoppers with an aluminum overseal.

Each vial of Cleviprex contains 0.5 mg/mL clevidipine butyrate, 200 mg/mL soybean oil USP, 22.5 mg/mL glycerin USP, 12 mg/mL purified egg yolk phospholipids, sodium hydroxide NF adjust pH to 6.0 - \_\_\_\_\_ and water for injection USP to 1 mL. Each bottle has an overfill of \_\_\_\_\_

The drug product is manufactured by Hospira, described in DMF \_\_\_\_\_, using standard processing techniques including \_\_\_\_\_ packaging, and shipping.

Specification of the drug product includes:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_ All test methods have been appropriately validated for their intended purpose.

Adequate stability data is provided to support storage of the 50 mL fill size at 2°C-8°C for 24 months and the 100 mL fill size at 2°C-8°C for 36 months. For "In-Use" storage, both sizes can remain up to 2 months at controlled room temperature, 20°-25°C (68°-77°F), with excursions from 15°C to 30°C, protected from light.

**Conclusion:** Drug product is acceptable.

**Additional Items:**

The analytical methods used in the testing procedures (release, stability, and in-process) are well known and widely used by the pharmaceutical industry and revalidation by Agency laboratories will not be requested.

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

/ / / / /

**Overall Conclusion:**

From a CMC perspective, the application is recommended for **Approval**.

Include the following in the action letter:

"Based on your drug product stability data, an expiration date of 24 months is granted for the 50 mL fill size when stored refrigerated (2 – 8°C). A 36 month shelf-life is granted for the 100 mL fill size when stored refrigerated. Both configurations can be stored for up to 2 months at controlled room temperature as "in-use" storage."

Blair A. Fraser, Ph.D.  
Director  
DPA I/ONDQA

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

/s/

-----  
Blair Fraser  
7/17/2008 11:10:28 AM  
CHEMIST



**NDA 22-156**

**Cleviprex™ (clevidipine butyrate)  
Injectable Emulsion**

**The Medicines Company**

**Division of Cardiovascular and Renal Products  
FDA CDER**

**Monica D. Cooper, Ph.D.  
ONDQA Pre-Marketing Assessment  
Division I/Branch I**

- and -

**H. Ted Chang, Ph.D.  
ONDQA Pre-Marketing Assessment and  
Manufacturing Science Division III/Branch VI**



# Table of Contents

|   |           |
|---|-----------|
| <b>Table of Contents .....</b>  | <b>2</b>  |
| <b>Chemistry Review Data Sheet.....</b>   | <b>4</b>  |
| <b>The Executive Summary .....</b>  | <b>9</b>  |
| <b>I. Recommendations .....</b>   | <b>9</b>  |
| A. Recommendation and Conclusion on Approvability.....  | 9         |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 9         |
| <b>II. Summary of Chemistry Assessments.....</b>  | <b>9</b>  |
| A. Description of the Drug Product(s) and Drug Substance(s) .....   | 9         |
| B. Description of How the Drug Product is Intended to be Used.....  | 11        |
| C. Basis for Approvability or Not-Approval Recommendation.....  | 11        |
| <b>III. Administrative.....</b>   | <b>11</b> |
| A. Reviewer's Signature.....  | 11        |
| B. Endorsement Block.....   | 11        |
| C. CC Block .....   | 11        |
| <b>Chemistry Assessment .....</b>   | <b>12</b> |
| <b>I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data.....</b>                             | <b>12</b> |
| <b>S DRUG SUBSTANCE [clevidipine butyrate, .....</b>  | <b>12</b> |
| S.1 General Information [clevidipine butyrate, .....  | 12        |
| S.2 Manufacture [clevidipine butyrate .....   | 12        |
| S.3 Characterization [clevidipine butyrate, .....   | 12        |
| S.4 Control of Drug Substance [clevidipine butyrate, .....  | 12        |
| S.5 Reference Standards or Materials [clevidipine butyrate, .....   | 14        |
| S.6 Container Closure System [clevidipine butyrate, .....   | 14        |
| S.7 Stability [clevidipine butyrate, .....  | 14        |
| <b>P DRUG PRODUCT.....</b>  | <b>15</b> |
| P.1 Description and Composition of the Drug Product .....   | 15        |
| P.2 Pharmaceutical Development.....   | 15        |
| P.3 Manufacture .....   | 15        |
| P.4 Control of Excipients .....   | 15        |
| P.5 Control of Drug Product.....  | 15        |
| P.6 Reference Standards or Materials.....   | 19        |
| P.7 Container Closure System.....   | 19        |
| P.8 Stability.....  | 19        |



# CHEMISTRY REVIEW



|      |  |    |
|------|--|----|
| A    | APPENDICES .....   | 21 |
| A.1  | Facilities and Equipment (biotech only).....                       | 21 |
| A.2  | Adventitious Agents Safety Evaluation.....                         | 21 |
| A.3  | Novel Excipients .....   | 21 |
| R    | REGIONAL INFORMATION .....   | 22 |
| R.1  | Executed Batch Records.....  | 22 |
| R.2  | Comparability Protocols.....                                       | 22 |
| R.3  | Methods Validation Package.....                                    | 22 |
| II.  | Review of Common Technical Document-Quality (Ctd-Q) Module 1 ..... | 22 |
| A.   | Labeling & Package Insert.....                                     | 22 |
| B.   | Environmental Assessment or Claim of Categorical Exclusion .....   | 26 |
| III. | Establishment Evaluation Report.....                               | 26 |
| IV.  | List of Deficiencies .....   | 26 |

**APPEARS THIS WAY  
ON ORIGINAL**



# Chemistry Review Data Sheet

1. NDA 22-156
2. REVIEW #: 2
3. REVIEW DATE: 24-Jun-2008
4. REVIEWERS: Monica Cooper, Ph.D. and H. Ted Chang, Ph.D.
5. PREVIOUS DOCUMENTS:

| Previous Documents  | Document Date |
|---------------------|---------------|
| NDA 22-156 (N000)   | 02-Jul-2007   |
| Amendment (N000 BC) | 25-Jul-2007   |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|------------------------|---------------|
| Amendment (N000 BL)    | 28-Mar-2008   |
| Amendment (N000 BZ)    | 18-Apr-2008   |
| Amendment (N000 BZ)    | 30-May-2008   |

7. NAME & ADDRESS OF APPLICANT:

|                       |  |
|-----------------------|--|
| <b>Name</b>           | The Medicines Company (TMC or MDCO)    |
| <b>Address</b>        | 8 Campus Drive<br>Parsippany, NJ 07054 |
| <b>Representative</b> | Gregory Williams                       |
| <b>Telephone</b>      | 973-647-6010                           |

8. DRUG PRODUCT NAME/CODE/TYPE:

|                                    |                    |
|------------------------------------|--------------------|
| <b>Proprietary Name</b>            | Cleviprex™         |
| <b>Non-Proprietary Name (USAN)</b> | Clevipine butyrate |
| <b>Code Names</b>                  | 2930.D and H324/38 |
| <b>Chemistry Type</b>              | 1                  |
| <b>Submission Priority</b>         | S                  |



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: L-type Calcium Channel Antagonist  
(1,4-dihydropyridine)
11. DOSAGE FORM: Sterile Injectable Emulsion
12. STRENGTH/POTENCY: 0.5 mg/mL (Bottles: 25 mg/50 mL  
and 50 mg/100 mL)
13. ROUTE OF ADMINISTRATION: Intravenous Infusion
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product

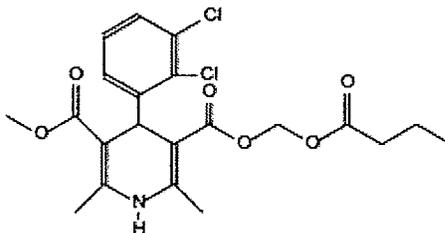
**APPEARS THIS WAY  
ON ORIGINAL**

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Chemical Names: Butyroxymethyl methyl 4-(2',3'-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

4-(2',3'-Dichlorophenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid, 3-butyryloxymethyl ester 5-methyl ester

US Adopted Name (USAN): clevidipine butyrate  
International Non-proprietary Name (INN): clevidipine  
Laboratory Codes: 2930.D and H324/38



Chemical Formula:  $C_{21}H_{23}Cl_2NO_6$   
Molecular Weight: 456.3  
CAS Number: 167221-71-8

**APPEARS THIS WAY  
ON ORIGINAL**



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

| DMF # | TYPE | HOLDER        | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED      |
|-------|------|---------------|-----------------|-------------------|---------------------|----------------------------|
| /     | II   | /             | Drug Substance  | 1                 | Adequate            | 23-Jun-2008<br>(M. Cooper) |
| /     | II   | Hospira, Inc. | Drug Product    | 1                 | Adequate            | 23-Jun-2008<br>(T. Chang)  |
| /     | IV   | /             | /               | 1                 | Adequate            | 11-Feb-2008<br>(T. Chang)  |

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under “Comments”)

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION                     |
|----------|--------------------|---------------------------------|
| IND      | 65,114             | Clevipidine Injection (H324/38) |



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 18. STATUS:

| CONSULTS & CMC RELATED REVIEWS | RECOMMENDATION  | DATE             | REVIEWER    |
|--------------------------------|---|------------------|-------------|
| EES                            | Acceptable  | 03-Aug-2007      | S. Ferguson |
| LNC                            | N/A   | ----             | ----        |
| Methods Validation             | Not Necessary   | ----             | ----        |
| OSE DMETS                      | Tradename: Cleviprex™<br>Acceptable   | 20-Dec-2007      | F. Duffy    |
| EA                             | Categorical Exclusion:<br>Acceptable  | See Review<br>#1 | M. Cooper   |
| Microbiology                   | Approvable, pending receipt<br>of additional information –<br>was resolved through labeling | 30-Apr-2008      | R. Mello    |

**APPEARS THIS WAY  
ON ORIGINAL**



# The Chemistry Review for NDA 22-156

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This new drug application (22-156) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. The deficiencies noted in CMC Review #1 have been addressed by the applicant. In addition, DMF \_\_\_\_\_ for the drug substance and DMF \_\_\_\_\_ for the drug product have been amended and are now adequate to support this NDA.

A consult to Microbiology was determined to be Approvable, pending receipt of additional information. However, the issue was resolved through labeling.

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities. The Establishment Evaluation Report is attached at the end of this review.

*The action letter should state –*

- Based on your drug product stability data, **an expiration date of 24 months is granted for the 50 mL fill size when stored refrigerated (2 – 8°C). A 36 month shelf-life is granted for the 100 mL fill size when stored refrigerated.** Both configurations can be stored for up to 2 months at controlled room temperature as “in-use” storage.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Clevudipine butyrate is a 1,4-dihydropyridine L-type calcium channel blocker. This new molecular entity (NME) drug has been formulated into an oil-in-water emulsion for intravenous injection and is indicated for \_\_\_\_\_ when use of an oral agent is not feasible or not desirable.

Drug Substance

The drug substance, clevidipine butyrate, is a chemically synthesized small molecule with one stereocenter. It is manufactured as a racemic mixture of (+)-S and (-)-R enantiomers. The chirality is caused by the asymmetrically substituted benzylic carbon. Both enantiomers have been shown to have similar pharmacological activity. Clevidipine butyrate is \_\_\_\_\_ that is practically insoluble in water.

Clevidipine butyrate is manufactured by \_\_\_\_\_. The manufacture, testing, and control of the drug substance is described in \_\_\_\_\_ DMF \_\_\_\_\_ - see DMF Reviews #1 and #2 (M. Cooper) for details. The applicant (and DMF holder) proposed a \_\_\_\_\_ retest date based on 36 months of long-term (25°C/60% RH) and 6 months of accelerated (40°C/75% RH) stability data. Based on the data provided in DMF \_\_\_\_\_, a retest date of \_\_\_\_\_ is appropriate when the drug substance is stored at controlled room temperature, protected from light.

Drug Product

The drug product—Clevidipine Emulsion—is a milky-white opaque oil-in-water emulsion at 0.5 mg/mL (clevidipine butyrate) strength presented in 50- (25 mg) and 100-mL (50 mg) bottles. The drug product is manufactured by \_\_\_\_\_

product. The drug products are stored at controlled temperature at 2°C-8°C and protected from light before use.

The manufacturing process is described entirely in DMF \_\_\_\_\_ (Holder: Hospira, Inc.)—see DMF Review #1 (T. Chang) for details.

\_\_\_\_\_ The applicant (and DMF holder) proposed a 36-month shelf-life for \_\_\_\_\_ (100 mL) at refrigerated conditions (2 – 8°C) based on up to 24-months of stability data for the 50-mL fill size, and up to 30-months of stability data for the 100-mL fill size. The applicant also proposed a 2-month “in-use” storage at 25°C±2°C after stored at the refrigerated temperature of 2°-8°C. **The proposed 36-month shelf-life at 2 – 8°C with a 2-month “in-use” (25°C) storage is acceptable for the 100-mL fill size only. A 24-month refrigerated shelf-life (with a 2-month “in-use” storage) should be granted for the 50-mL fill size.** The 24-month expiration date



Executive Summary Section

for the 50-mL vial size was determined through statistical analysis of the impurities data by the Office of Biostatistics (informal consult to Roswitha Kelly, Ph.D.).

**B. Description of How the Drug Product is Intended to be Used**

The applicant stated that Clevidipine Emulsion \_\_\_\_\_, No dilution or reconstitution is necessary.

**C. Basis for Approvability or Not-Approval Recommendation**

This new drug application (22-156) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. The deficiencies noted in CMC Review #1 of the NDA and in the reviews of the DMF for the drug substance (DMF \_\_\_\_\_) and the DMF for the drug product (DMF \_\_\_\_\_) have been resolved.

**III. Administrative**

**A. Reviewer's Signature**

/s/ M. D. Cooper, Ph.D.

/s/ H. T. Chang, Ph.D.

**B. Endorsement Block**

|                                      |                              |
|--------------------------------------|------------------------------|
| Chemistry Reviewer (drug substance): | Monica D. Cooper, Ph.D.      |
| Chemistry Reviewer (drug product):   | H. Ted Chang, Ph.D.          |
| Pharmaceutical Assessment Lead:      | Kasturi Srinivasachar, Ph.D. |
| Branch Chief:                        | Ramesh Sood, Ph.D.           |
| Project Manager:                     | Alisea Sermon, Pharm.D.      |

**C. CC Block**

Orig. NDA 22-156  
HFD-110/Division File

15 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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

/s/

-----  
Monica Cooper

6/24/2008 11:17:33 AM

CHEMIST

Entered on behalf of myself (drug substance reviewer) and  
Ted Chang, Ph.D. (drug product reviewer).

Ramesh Sood

6/24/2008 11:55:47 AM

CHEMIST

146 Page(s) Withheld

     Trade Secret / Confidential

     Draft Labeling

     Deliberative Process



**NDA 22-156**

**Cleviprex™ (clevidipine butyrate)  
Injectable Emulsion**

**The Medicines Company**

**Division of Cardiovascular and Renal Products  
FDA CDER**

**Monica D. Cooper, Ph.D.  
ONDQA Pre-Marketing Assessment  
Division I/Branch I**

- and -

**Ted Chang, Ph.D.  
ONDQA Pre-Marketing Assessment and  
Manufacturing Science Division III/Branch VI**



# Table of Contents

|   |           |
|---|-----------|
| <b>Table of Contents .....</b>  | <b>2</b>  |
| <b>Chemistry Review Data Sheet.....</b>   | <b>4</b>  |
| <b>The Executive Summary .....</b>  | <b>9</b>  |
| <b>I. Recommendations .....</b>   | <b>9</b>  |
| A. Recommendation and Conclusion on Approvability .....   | 9         |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 9         |
| <b>II. Summary of Chemistry Assessments.....</b>  | <b>9</b>  |
| A. Description of the Drug Product(s) and Drug Substance(s).....  | 9         |
| B. Description of How the Drug Product is Intended to be Used.....  | 10        |
| C. Basis for Approvability or Not-Approval Recommendation.....  | 11        |
| <b>III. Administrative.....</b>   | <b>11</b> |
| A. Reviewer's Signature.....  | 11        |
| B. Endorsement Block.....   | 11        |
| C. CC Block .....   | 11        |
| <b>Chemistry Assessment.....</b>  | <b>12</b> |
| <b>I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data.....</b>                             | <b>12</b> |
| <b>S DRUG SUBSTANCE [clevidipine butyrate .....</b>   | <b>12</b> |
| S.1 General Information [clevidipine butyrate, .....  | 12        |
| S.2 Manufacture [clevidipine butyrate, .....  | 13        |
| S.3 Characterization [clevidipine butyrate, .....   | 18        |
| S.4 Control of Drug Substance [clevidipine butyrate, .....  | 21        |
| S.5 Reference Standards or Materials [clevidipine butyrate, .....   | 24        |
| S.6 Container Closure System [clevidipine butyrate, .....   | 24        |
| S.7 Stability [clevidipine butyrate .....   | 25        |
| <b>P DRUG PRODUCT.....</b>  | <b>27</b> |
| P.1 Description and Composition of the Drug Product .....   | 27        |
| P.2 Pharmaceutical Development.....   | 28        |
| P.3 Manufacture .....   | 33        |
| P.4 Control of Excipients .....   | 36        |
| P.5 Control of Drug Product.....  | 36        |
| P.6 Reference Standards or Materials.....   | 49        |
| P.7 Container Closure System.....   | 49        |
| P.8 Stability .....   | 49        |



# CHEMISTRY REVIEW



|      |   |    |
|------|---|----|
| A    | APPENDICES .....  | 57 |
| A.1  | Facilities and Equipment (biotech only).....                        | 57 |
| A.2  | Adventitious Agents Safety Evaluation.....                          | 57 |
| A.3  | Novel Excipients .....  | 57 |
| R    | REGIONAL INFORMATION .....  | 58 |
| R.1  | Executed Batch Records.....   | 58 |
| R.2  | Comparability Protocols.....  | 58 |
| R.3  | Methods Validation Package.....                                     | 60 |
| II.  | Review of Common Technical Document-Quality (Ctd-Q) Module 1 .....  | 60 |
| A.   | Labeling & Package Insert.....                                      | 60 |
| B.   | Environmental Assessment or Claim of Categorical Exclusion .....    | 63 |
| III. | Establishment Evaluation Report.....                                | 65 |
| IV.  | List of Deficiencies Communicated to Applicant on 25-Feb-2008 ..... | 70 |

**APPEARS THIS WAY  
ON ORIGINAL**



# Chemistry Review Data Sheet

1. NDA 22-156
2. REVIEW #: 1
3. REVIEW DATE: 04-Mar-2008
4. REVIEWERS: Monica Cooper, Ph.D. and Ted Chang, Ph.D.
5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|--------------------|---------------|
| None               |               |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|------------------------|---------------|
| NDA 22-156 (N000)      | 02-Jul-2007   |
| Amendment (N000 BC)    | 25-Jul-2007   |

7. NAME & ADDRESS OF APPLICANT:

|                       |  |
|-----------------------|--|
| <b>Name</b>           | The Medicines Company (TMC)            |
| <b>Address</b>        | 8 Campus Drive<br>Parsippany, NJ 07054 |
| <b>Representative</b> | Gregory Williams                       |
| <b>Telephone</b>      | 973-647-6010                           |

8. DRUG PRODUCT NAME/CODE/TYPE:

|                                    |                    |
|------------------------------------|--------------------|
| <b>Proprietary Name</b>            | Cleviprex™         |
| <b>Non-Proprietary Name (USAN)</b> | Clevipine butyrate |
| <b>Code Names</b>                  | 2930.D and H324/38 |
| <b>Chemistry Type</b>              | 1                  |
| <b>Submission Priority</b>         | S                  |



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: L-type Calcium Channel Antagonist  
(1,4-dihydropyridine)
11. DOSAGE FORM: Sterile Injectable Emulsion
12. STRENGTH/POTENCY: 0.5 mg/mL (Bottles: 25-mg/50 mL  
and 50-mg/100 mL)
13. ROUTE OF ADMINISTRATION: Intravenous Infusion
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product

APPEARS THIS WAY  
ON ORIGINAL



## CHEMISTRY REVIEW



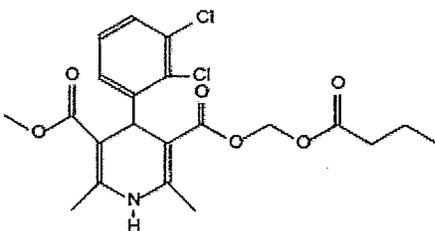
### Chemistry Review Data Sheet

#### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: Butyroxymethyl methyl 4-(2',3'-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

4-(2',3'-Dichlorophenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid, 3-butyryloxymethyl ester 5-methyl ester

US Adopted Name (USAN): clevidipine butyrate  
International Non-proprietary Name (INN): clevidipine  
Laboratory Codes: 2930.D and H324/38



Chemical Formula:  $C_{21}H_{23}Cl_2NO_6$   
Molecular Weight: 456.3  
CAS Number: 167221-71-8

**APPEARS THIS WAY  
ON ORIGINAL**

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

| DMF# | TYPE | HOLDER        | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED      |
|------|------|---------------|-----------------|-------------------|---------------------|----------------------------|
| —    | II   | /             | Drug Substance  | 1                 | Inadequate          | 16-Jan-2008<br>(M. Cooper) |
| —    | II   | Hospira, Inc. | Drug Product    | 1                 | Inadequate          | 20-Feb-2008<br>(T. Chang)  |
| —    | IV   | /             | /               | 1                 | Adequate            | 11-Feb-2008<br>(T. Chang)  |

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under “Comments”)

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION                     |
|----------|--------------------|---------------------------------|
| IND      | 65,114             | Clevidipine Injection (H324/38) |



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 18. STATUS:

| CONSULTS &<br>CMC RELATED<br>REVIEWS | RECOMMENDATION                       | DATE                     | REVIEWER    |
|--------------------------------------|--------------------------------------|--------------------------|-------------|
| EES                                  | Acceptable                           | 03-Aug-2007              | S. Ferguson |
| LNC                                  | N/A                                  | ----                     | ----        |
| Methods Validation                   | <i>to be initiated post approval</i> | ----                     | ----        |
| OSE DMETS                            | Tradename: Cleviprex™<br>ACCEPTABLE  | 20-Dec-2007              | F. Duffy    |
| EA                                   | Categorical Exclusion:<br>Acceptable | See Review<br>Date above | M. Cooper   |
| Microbiology                         | Pending                              |                          | R. Mello    |

**APPEARS THIS WAY  
ON ORIGINAL**



# The Chemistry Review for NDA 22-156

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This new drug application (22-156) is **APPROVABLE** from the perspective of chemistry, manufacturing, and controls. Several deficiencies have been noted at the end of this review, which were sent to the applicant. In addition, DMF \_\_\_\_\_ for the drug substance and DMF \_\_\_\_\_ for the drug product are not adequate to support this NDA.

A consult to Microbiology is currently PENDING.

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities. The Establishment Evaluation Report is attached at the end of this review.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Clevudipine butyrate is a 1,4-dihydropyridine L-type calcium channel blocker. This new molecular entity (NME) drug has been formulated into an oil-in-water emulsion for intravenous injection and is indicated for the \_\_\_\_\_ when use of an oral agent is not feasible or not desirable.

##### Drug Substance

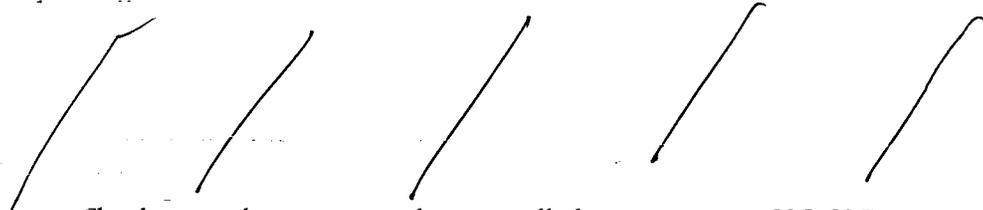
The drug substance, clevudipine butyrate, is a chemically synthesized small molecule with one stereocenter. It is manufactured as a racemic mixture of (+)-S and (-)-R enantiomers. The chirality is caused by the asymmetrically substituted benzylic carbon. Both enantiomers have been shown to have similar pharmacological activity. Clevudipine butyrate is a \_\_\_\_\_ that is practically insoluble in water, ; \_\_\_\_\_

Executive Summary Section

Clevipidine butyrate is manufactured by [redacted]. The manufacture, testing, and control of the drug substance is described in [redacted] DMF [redacted] - see DMF Review #1 (M. Cooper) for details. The applicant (and DMF holder) proposed a [redacted] retest date based on 36 months of long-term (25°C/60% RH) and 6 months of accelerated (40°C/75% RH) stability data. Based on the data provided in DMF [redacted] a retest date of [redacted] is appropriate when the drug substance is stored at controlled room temperature, protected from light.

Drug Product

The drug product—Clevipidine Emulsion—is a milky-white opaque oil-in-water emulsion at 0.5 mg/mL (clevipidine butyrate) strength presented in 50- (25 mg) and 100-mL (50 mg) bottles. The drug product is manufactured by [redacted]



The drug products are stored at controlled temperature at 2°C-8°C and protected from light before use.

The manufacturing process is described entirely in DMF [redacted] (Holder: Hospira, Inc.)—see DMF Review #1 (T. Chang) for details. [redacted]

[redacted] The applicant (and DMF holder) proposed [redacted] shelf-life based on up to 30-month stability data. Additional data will be submitted in amendment. The applicant also proposed a 2-month “in-use” storage at 25°C±2°C after stored at the refrigerated temperature of 2°C-8°C.

B. Description of How the Drug Product is Intended to be Used

The applicant stated that Clevipidine Emulsion [redacted] No dilution or reconstitution is necessary.





Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

This new drug application (22-156) is **APPROVABLE** from the perspective of chemistry, manufacturing, and controls due to several deficiencies in the NDA (see list at the end of this review) and in the DMF for the drug substance (DMF       ) and the DMF for the drug product (DMF       ). This application was determined to be “approvable” rather than “not approvable” because the applicant should be able to resolve the deficiencies readily.

**III. Administrative**

**A. Reviewer’s Signature**

/s/ M.D. Cooper, Ph.D.

/s/ H. T. Chang, Ph.D.

**B. Endorsement Block**

|                                      |                              |
|--------------------------------------|------------------------------|
| Chemistry Reviewer (drug substance): | Monica D. Cooper, Ph.D.      |
| Chemistry Reviewer (drug product):   | H. Ted Chang, Ph.D.          |
| Pharmaceutical Assessment Lead:      | Kasturi Srinivasachar, Ph.D. |
| Branch Chief:                        | Ramesh Sood, Ph.D.           |
| Project Manager:                     | Denise Hinton                |

**C. CC Block**

Orig. NDA 22-156  
HFD-110/Division File

66 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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

/s/  
-----

Monica Cooper  
3/4/2008 04:50:49 PM  
CHEMIST

Ted Chang  
3/5/2008 07:39:06 AM  
CHEMIST

Ramesh Sood  
3/5/2008 08:57:19 AM  
CHEMIST

7 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Initial Quality Assessment  
Branch I

**OND Division:** Division of Cardiovascular and Renal Products  
**NDA:** 22-156  
**Applicant:** The Medicines Company  
**Letter Date:** 2 Jul 2007  
**Stamp Date:** 2 Jul 2007  
**PDUFA Date:** 2 Jan 2008 (Priority)  
**Tradename:** Cleviprex  
**Established Name:** Clevidipine butyrate  
**Dosage Form:** Sterile emulsion, 0.5 mg/mL  
**Route of Administration:** Intravenous injection  
**Indication:** \_\_\_\_\_ when use of an oral agent is not feasible or not desirable.

**Assessed by:** Kasturi Srinivasachar  
**ONDQA Fileability:** Yes  
**Comments for 74-Day Letter:** See Labeling issues under Comments and Recommendations

**Summary**

This NDA is an eCTD submission for a new molecular entity. Clevidipine butyrate is a 1,4-dihydropyridine calcium channel antagonist which has been formulated by the Applicant as an oil-in-water emulsion for intravenous administration. The drug product contains soybean oil, glycerin and purified egg yolk phospholipids as excipients and sodium hydroxide for pH adjustment. The majority of the CMC information for drug substance and drug product resides in DMFs \_\_\_\_\_ and \_\_\_\_\_ respectively.

The clinical program in support of this NDA was conducted under IND application 65,114. There were no CMC specific meetings with the Applicant and only one CMC issue has been discussed in an interdisciplinary pre-NDA meeting held on Jan. 30, 2007. The Applicant proposed deleting assays for soybean oil, glycerin and phospholipids from the drug product specifications but were advised to retain these tests since these excipients are critical components of the emulsion formulation.

**Drug Substance**

Clevidipine is a synthetic compound with one asymmetric center which is manufactured as a racemic mixture. It is practically insoluble in water! \_\_\_\_\_

\_\_\_\_\_ and details are provided in DMF \_\_\_\_\_. The updated submission of Nov. 2006 is in CTD format. This DMF has not been previously reviewed. A retest date of \_\_\_\_\_ is proposed for the drug substance packaged in \_\_\_\_\_ bags and stored in \_\_\_\_\_ containers at 25°C.

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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

/s/

-----  
Kasturi Srinivasachar  
7/27/2007 12:13:55 PM  
CHEMIST

Ramesh Sood  
7/27/2007 01:48:12 PM  
CHEMIST

**Division of Cardio-Renal Drug Products**  
Review of Chemistry, Manufacturing, and Controls

IND #: 65,114

CHEM. REVIEW #: 2

REVIEW DATE: 06-Feb-2003

SUBMISSION TYPE

Amendment (N002 IC), Phase II

DOCUMENT DATE

06-Dec-2002

CDER DATE

09-Dec-2002

CHEMISTRY REVIEWER:

Monica D. Cooper  
DNDCL, HFD-110

DRUG NAME:

Clevidipine Injection (H324/38  
Emulsion for Infusion)

NAME AND ADDRESS OF SPONSOR:

The Medicines Company  
One Cambridge Center  
Cambridge, MA 02142

PHARMACOL. CATEGORY/INDICATION:

Calcium Channel Blocker/

DOSAGE FORM/STRENGTHS:

Injectable Emulsion/ 0.5 mg/mL

ROUTE OF ADMINISTRATION:

Intravenous via an Infusion Pump

SPECIAL PRODUCTS:

No

PLACEBO:

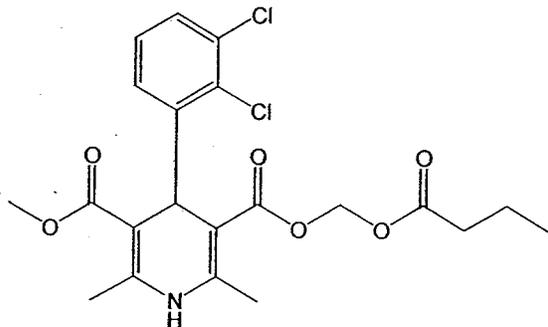
Yes, Intralipid®

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA & MOLECULAR WEIGHT:

Butyroxymethyl methyl 4-(2',3'-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

$C_{21}H_{23}Cl_2NO_6$

MW: 456.3



DRAFT PORTION OF LETTER ATTACHED: No

RELATED DOCUMENTS:

IND 50,261  
DMF

IND #65,114  
Page 2  
Review #2

**MANUFACTURERS:**

References to AstraZeneca's IND 50,261 and \_\_\_\_\_ DMF \_\_\_\_\_ have been made regarding the CMC data for the drug substance and the drug product.

**COMMENTS:**

This Amendment (N002 PC/IC) contains a clinical change in protocol, as well as a CMC information update. The clinical portion of this Amendment is referred to the medical officer (M. Desai). This review summarizes and evaluates the CMC portion only.

The sponsor stated that they will now provide the placebo (Intralipid®) for the clinical study rather than having the sites acquire it from hospital stock, as previously indicated. The sponsor included a copy of the COA for one lot of Intralipid®, which confirmed the lack of active (clevidipine) using HPLC.

Per a teleconference with our Division on 01-Aug-2002, the sponsor enclosed the results of additional stability studies of clevidipine bulk drug substance, which had been performed by AstraZeneca under IND 50,261. The drug substance was tested for \_\_\_\_\_

\_\_\_\_\_ Four batches were tested – one batch for 6.5 months, two batches for 36 months, and one batch for 39 months. Specifications were not provided for the tests performed. However, the following drug substance specifications had been provided in IND 50,261:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Thus, it was noted that batch 300/94 stored in \_\_\_\_\_ vials at 30°C/75%RH went below the specification limit for Assay at 24 months. However, this batch did not go out of specification at 25°C/60%RH for up to 36 months.

**Overall Evaluation and Recommendations: ACCEPTABLE.** No action is necessary at this time.

IND 65,114  
HFD-110 Division File  
HFD-110 Monica Cooper  
HFD-110 Project Manager, D. Hinton

\_\_\_\_\_  
Review Chemist,  
Monica D. Cooper

\_\_\_\_\_  
Team Leader,  
Kasturi Srinivasachar

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

/s/

-----  
Monica Cooper  
4/3/03 06:52:46 PM  
CHEMIST

Kasturi Srinivasachar  
4/4/03 03:16:35 PM  
CHEMIST

**Division of Cardio-Renal Drug Products**  
Review of Chemistry, Manufacturing, and Controls

IND #: 65,114

CHEM. REVIEW #: 1

REVIEW DATE: 26-Aug-2002

**SUBMISSION TYPE**  
Original (#000), Phase II

**DOCUMENT DATE**  
26-June-2002

**CDER DATE**  
27-June-2002

**ASSIGNED DATE**  
03-July-2002

**CHEMISTRY REVIEWER:**

Monica D. Cooper  
DNDCL, HFD-110

**DRUG NAME:**

Clevidipine Injection (H324/38  
Emulsion for Infusion)

**NAME AND ADDRESS OF SPONSOR:**

The Medicines Company  
One Cambridge Center  
Cambridge, MA 02142

**PHARMACOL. CATEGORY/INDICATION:**

Calcium Channel Blocker/  

---

**DOSAGE FORM/STRENGTHS:**

Injectable Emulsion/ 0.5 mg/mL

**ROUTE OF ADMINISTRATION:**

Intravenous via an Infusion Pump

**SPECIAL PRODUCTS:**

No

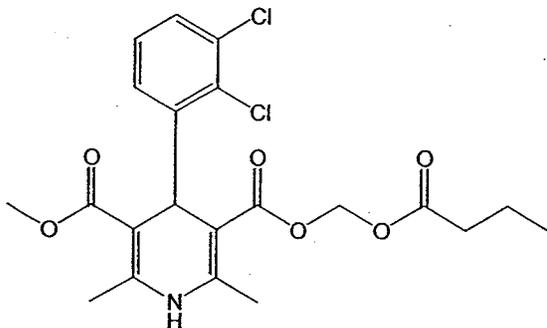
**PLACEBO:**

No

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA & MOLECULAR WEIGHT:**

Butyroxymethyl methyl 4-(2',3'-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

$C_{21}H_{23}Cl_2NO_6$   
MW: 456.3



IND #65,114  
 Page 2  
 Review #1

**MANUFACTURERS:**

References to AstraZeneca's IND 50,261 and \_\_\_\_\_ DMF \_\_\_\_\_ have been made regarding the CMC data for the drug substance and the drug product.

**DRAFT PORTION OF LETTER ATTACHED:** No

**RELATED DOCUMENTS:** IND 50,261  
 DMF \_\_\_\_\_

**III. REVIEW**

| ATTRIBUTE/METHODS                    | Adequate Information Provided: |                |                                 |                |
|--------------------------------------|--------------------------------|----------------|---------------------------------|----------------|
|                                      | DRUG SUBSTANCE                 |                | DRUG PRODUCT                    |                |
|                                      | YES ( Vol, Page)               | NO (Vol, Page) | YES (Vol, Page)                 | NO (Vol, Page) |
| Synthesis/Manufacturing              | See IND 50,261                 |                |                                 |                |
| Identity                             | See IND 50,261                 |                |                                 |                |
| Purity Profile                       | See IND 50,261                 |                |                                 |                |
| Strength/Assay                       |                                |                | See IND 50,261<br>and DMF _____ |                |
| <b>FOR PARENTERAL DRUG PRODUCTS:</b> |                                |                |                                 |                |
| _____                                |                                |                |                                 | ✓              |
| _____                                |                                |                | See DMF _____                   |                |
| _____                                |                                |                | See DMF _____                   |                |
| _____                                |                                |                | See DMF _____                   |                |
| _____                                |                                |                | See DMF _____                   |                |

**Comments:**

This is a Phase II trial to examine the effect of clevidipine for short-term control of high blood pressure in the perioperative setting, involving 102 patients. This is a double-blind, multi-center, randomized comparison of clevidipine versus nitroglycerin for blood pressure control and preservation of renal function in patients undergoing elective Coronary Artery Bypass Graft (CABG) surgery. The treatment will last from induction of anesthesia until 12 hours postoperatively for both clevidipine and nitroglycerin. The primary objective of the study is to compare blood pressure control in patients undergoing CABG surgery who are intra- and post-operatively administered clevidipine or nitroglycerin (which is the most commonly used agent to control blood pressure and ischemia during and after cardiac surgery). The secondary objective is to \_\_\_\_\_

Clevidipine is an \_\_\_\_\_ vascular-selective calcium antagonist, intended for \_\_\_\_\_ intravenous control of blood pressure \_\_\_\_\_. It reduces arterial blood pressure dose-dependently by reduction of systemic vascular resistance. Clevidipine is practically insoluble in water, \_\_\_\_\_, clevidipine injection (0.5 mg/mL) is an emulsion of \_\_\_\_\_ soybean oil.

IND #65,114  
Page 3  
Review #1

The Chemistry, Manufacturing, and Controls data for the Drug Substance and the Drug Product are referenced to IND 50,261 from AstraZeneca and to DMF \_\_\_\_\_ from \_\_\_\_\_. The IND 50,261 was reviewed by Joseph T. Piechocki on 14-Jun-1996 and a deficiency letter was sent on 03-Sep-1996. The company sent their response on 09-Apr-1997. This reviewer found the response to be adequate. A review of the updated materials submitted to DMF \_\_\_\_\_ was completed and found to be adequate by this reviewer in support of IND 65,114. The sponsor provided the following information to support this application -

- A letter from AstraZeneca LP authorizing The Medicines Company to refer to their IND 50,261.
- A letter from \_\_\_\_\_ authorizing The Medicines Company to refer to their DMF \_\_\_\_\_
- A letter from \_\_\_\_\_ to AstraZeneca notifying them of a manufacturing update filed in regard to DMF \_\_\_\_\_
- Copies of the bottle and carton labels to be used in the study, both including the cautionary statement: "New Drug - Limited by United States law to investigational use."
- A diagram of the carton to be used.
- A claim of categorical exemption under 21 CFR 25.31 (e) in regard to environmental assessment.

A placebo to match clevidipine is not being supplied by the sponsor. Instead, the commercially marketed product, Intralipid 20%, will be obtained from the hospital pharmacy stock and prepared by the study pharmacist, in order to maintain study blinding.

Questions: Regarding IND 50,261 (currently inactive due to \_\_\_\_\_) the following concerns were conveyed to the sponsor (Lisa-Sue Wood, 617-225-9099) in a telephone conference on Aug. 1, 2002. The firm's responses are in *Italics* below:

- The sponsor has not provided any information about the source of the starting material. \_\_\_\_\_ this compound does not appear to meet the criteria for appropriate starting materials outlined in the Drug Substance guidance. Hence, the starting material may not be acceptable in a future NDA submission.

*The sponsor will take this information into account.*

- DMF \_\_\_\_\_ states that a new shelf life (expiration date) for the drug substance was confirmed out to 24 months and referenced IND 50,261 for the drug substance stability data. However, IND 50,261 contains stability data for the drug substance only out to 14 months, to date. Thus, the expiration date of \_\_\_\_\_ not justified, given that expiration dating is based on real-time data. However, expiration dating is not a relevant issue at the IND stage. Stability data should cover the duration of the clinical trial.

*An amendment containing additional stability data for the drug substance will be submitted in the near future.*

- Intralipid, 20%, is a commercially available product for what indication? Has it been tested for lack of active?

*Intralipid is a nutritional product for parenteral feeding (an IV food). In the future, Intralipid will be supplied to the clinical investigators by the sponsor, rather than from the hospital pharmacy. An amendment will be submitted in the near future with more information on the placebo, including the results of the test for lack of active.*

-- Meeting Adjourned.

IND #65,114  
Page 4  
Review #1

T-con Attendees:

FDA

Monica Cooper, Ph.D., Chemist  
Kasturi Srinivasachar, Ph.D., Chemist

The Medicines Company

Lisa-Sue Wood, Regulatory Affairs  
Sonja Loar, Regulatory Affairs  
John Richards, Manufacturing  
Tom Wright, Manufacturing  
Pearl Hutchins, Quality

Conclusions and Recommendations:

**Based on the information provided, it is reasonably safe to initiate clinical studies from the standpoint of chemistry, manufacturing, and controls.**

IND 65,114  
HFD-110 Division File  
HFD-110 Monica Cooper  
HFD-110 Project Manager, D. Hinton

---

Review Chemist,  
Monica D. Cooper

---

Team Leader,  
Kasturi Srinivasachar

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

/s/

-----  
Monica Cooper  
8/26/02 05:17:21 PM  
CHEMIST

Kasturi Srinivasachar  
8/26/02 05:46:57 PM  
CHEMIST