

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-156

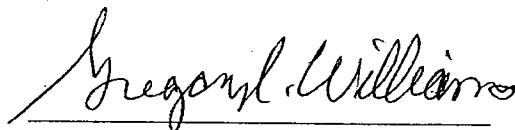
**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Patent Information

In accordance with 21 CFR 314.53 (c) (1), information about the claimed patent is listed below:

- (i) Patent number: 5,856,346; expiration date: January 5, 2016, and
- (ii) Type of patent: active ingredient, composition of matter/Drug and Pharmaceutical composition; methods of use/treatment, and composition of matter/Drug and Pharmaceutical composition; methods of use/treatment
- (iii) Name of Patent Owner: Astra Aktiebolag; The patent is exclusively licensed by the applicant, The Medicines Company
- (iv) AstraZenaca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850

The undersigned declares that Patent No. 5,856,346 covers the formulation, composition, and /or method of use of Cleviprex™ (clevidipine) IV emulsion. This product is the subject of this application for which approval is being sought.



THE MEDICINES COMPANY by
Gregory Williams, PhD
Vice President, Regulatory Affairs
and Program Management

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

122-156

NAME OF APPLICANT / NDA HOLDER

The Medicines Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Cleviprex™

ACTIVE INGREDIENT(S)

Clevidipine

STRENGTH(S)

50 mL bottle with 0.5 mg/mL Cleviprex™

100 mL bottle with 0.5 mg/mL Cleviprex™

DOSAGE FORM

Injection, emulsion

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

GENERAL

a. United States Patent Number

5,856,346

b. Issue Date of Patent

1/5/1999

c. Expiration Date of Patent

1/5/2016

d. Name of Patent Owner

Astra Aktiebolag

Address (of Patent Owner)

S-151 85

City/State

Sodertalje

ZIP Code

Sweden

FAX Number (if available)

Telephone Number

+46 (0)8 553 260 00

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

AstraZeneca Pharmaceuticals LP

Address (of agent or representative named in 1.e.)

1800 Concord Pike

City/State

Wilmington, Delaware

ZIP Code

19850

FAX Number (if available)

Telephone Number

(302) 886-3000

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

- 4.2 Patent Claim Number (as listed in the patent) 8 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
See Attachment

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration/Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed

Gregory P. Williams

7/2/07

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Greg Williams, Vice President, Regulatory Affairs and Program Management, The Medicines Company

Address

8 Campus Drive

City/State

Parsippany, New Jersey

ZIP Code

07054

Telephone Number

(973) 656-1616

FAX Number (if available)

(973) 656-9898

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Patent Information

In accordance with 21 CFR 314.53 (c) (1), information about the claimed patent(s) is listed below:

- (i) Patent number 5,739,152; expiration date: April 14, 2015
- (ii) Type of patent: active ingredient, composition of matter/Drug and Pharmaceutical composition; methods of use/treatment, and composition of matter/Drug and Pharmaceutical composition; methods of use/treatment
- (iii) Name of Patent Owner: Astra Aktiebolag; The patent is exclusively licensed by the applicant, The Medicines Company
- (iv) AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850

The undersigned declares that Patent No. 5,739,152 covers the formulation, composition, and /or method of use of Cleviprex™ (clevidipine) IV emulsion. This product is the subject of this application for which approval is being sought.



THE MEDICINES COMPANY by
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Vice President, Regulatory Affairs
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NDA NUMBER

22-156

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The Medicines Company

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TRADE NAME (OR PROPOSED TRADE NAME)

Cleviprex™

ACTIVE INGREDIENT(S)

Clevidipine

STRENGTH(S)

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100 mL bottle with 0.5 mg/mL Cleviprex™

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GENERAL

a. United States Patent Number

5,739,152

b. Issue Date of Patent

4/14/1998

c. Expiration Date of Patent

4/14/2015

d. Name of Patent Owner

Astra Aktiebolag

Address (of Patent Owner)

S-151 85

City/State

Sodertalje

ZIP Code

Sweden

FAX Number (if available)

Telephone Number

+46 (0)8 553 260 00

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

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- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed

Gregory L. Williams

7/2/07

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Greg Williams, Vice President, Regulatory Affairs and Program Management, The Medicines Company

Address

8 Campus Drive

City/State

Parsippany, New Jersey

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Telephone Number

(973) 656-1616

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22-156

SUPPL # N/A

HFD # 110

Trade Name N/A

Generic Name Clevidipine Butyrate Injection

Applicant Name The Medicines Company, Inc

Approval Date, If Known August 1, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Alisea Crowley
Title: Regulatory Health Project Manager
Date: 07/29/2008

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Norman Stockbridge
8/1/2008 02:38:45 PM

Statement of claimed exclusivity

The Medicines Company requests to claim exclusivity according to 21 CFR 314.50(j) for Cleviprex(tm) (clevidipine IV emulsion), a dihydropyridine calcium channel blocker indicated for the _____ when the use of oral therapy is not feasible or not desirable.

The Medicines Company requests five (5) year exclusivity according to 21 CFR 314.108(b)(2) which states "If a drug product that contains a new chemical entity was approved after September 24, 1984, in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application, except that the 505(b)(2) application or abbreviated application may be submitted after 4 years if it contains a certification of patent invalidity or non-infringement described in Section 314.50(i)(1)(i)(A)(4) or 314.94(a)(12)(i)(A)(4)".

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-156 Supplement

Stamp Date: 2Jul07 PDUFA Goal Date: 2May08

HFD-110 Trade and generic names/dosage form: Cleviprex (clevidipine butyrate) Injectable Emulsion 0.5 mg/mL

Applicant: The Medicines Company Therapeutic Class: Calcium Channel Blocker

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Cleviprex™ (clevidipine butyrate) Injectable Emulsion is a dihydropyridine calcium channel blocker indicated for _____ when the use of oral therapy is not feasible or not desirable.

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: ___ Partial Waiver Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

• Age _____
• _____
• _____

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: Based on the efficacy and safety data for clevidipine in adult studies involving acute hypertension subjects that are described in NDA # 22-156, the sponsor believes it is appropriate to investigate the clinical efficacy and safety of clevidipine in the pediatric acute hypertension population. As agreed at the Pre-NDA meeting on January 30, 2007, the sponsor complied with their commitment to have an outline of the planned pediatric study(ies) in place before approval of the clevidipine IV emulsion NDA.

Date studies are due (mm/dd/yy): None proposed at present. The conduct and submission of any pediatric studies that comprise the agreed pediatric plan will be a Phase IV commitment, following approval of the clevidipine IV emulsion NDA.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Denise M. Hinton
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

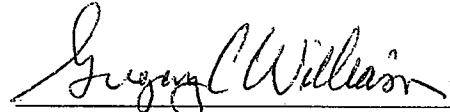
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Denise Hinton
3/13/2008 03:24:08 PM

Debarment Certification

On behalf of The Medicines Company, I hereby certify that we did not and will not knowingly use in any capacity the services of an individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA 22-156 for Cleviprex™ (clevipidine) IV emulsion.



THE MEDICINES COMPANY
Gregory C. Williams, Ph.D.
Vice President, Regulatory Affairs
and Program Management

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 22-156	Efficacy Supplement Type N/A	Supplement Number N/A
Drug: Cleviprex (clevidipine butyrate) Injection		Applicant: The Medicines Company, Inc.
RPM: Alisea Cowley, Pharm.D.		HFD- 110 Phone # (301) 796-1144
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
Chem class (NDAs only)		
Other (e.g., orphan, OTC)		
User Fee Goal Dates		August 2, 2008
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
User Fee Information		
User Fee		<input checked="" type="checkbox"/> Paid UF ID number PD3007175
User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify) _
❖ Application Integrity Policy (AIP)		
Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Exception for review (Center Director's memo)	
OC clearance for approval	
Paraphrase certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified
❖ Patent	
Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input type="checkbox"/> Verified
Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) (Verified) 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	
Answer the following questions for each paragraph IV certification:	
Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?	<input type="checkbox"/> Yes <input type="checkbox"/> No
(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).	
<i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i>	
Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i>	
<i>If "No," continue with question (3).</i>	
Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	<input type="checkbox"/> Yes <input type="checkbox"/> No
(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its	

representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<p>Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</p>	No
<p>Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</p>	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	August 1, 2008

❖ Actions	
Proposed action	(X) AP () TA () AE () NA
Previous actions (specify type and date for each action taken)	
Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
Press Office notified of action (approval only)	(X) Yes () Not applicable
Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
Division's proposed labeling (only if generated after latest applicant submission of labeling)	
Most recent applicant-proposed labeling	July 29, 2008
Original applicant-proposed labeling	July 2, 2007
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>) 	DMETS: 6/25/08; 12/20/07 DDMAC: 03/17/2007 Labeling Mtg. w/ Sponsor: 07/28/08
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
Applicant proposed	July 2, 2007
Reviews	See CMC & DMETS Reviews
Post-marketing commitments	
Agency request for post-marketing commitments	Pediatric Studies
Documentation of discussions and/or agreements relating to post-marketing commitments	
Outgoing correspondence (i.e., letters, E-mails, faxes)	ACK Letter- 07/17/07 Filing Letter- 09/13/07 User Fee Ext. Ltr-5/1/08 Discipline Review Ltr-02/25/08
Memoranda and Telecons	Labeling Discussion: 07/28/08
Minutes of Meetings	
EOP2 meeting (indicate date)	N/A
Pre-NDA meeting (indicate date)	03/01/2007
Pre-Approval Safety Conference (indicate date; approvals only)	07/28/2008 (Labeling Mtg. w/OSE)
Other-	
Advisory Committee Meeting	
Date of Meeting	
48-hour alert	
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Office Director: Division Director: 06/16/2008 Med Team Leader: 05/13/2008
❖ Clinical review(s) (indicate date for each review)	03/10/2008
❖ Microbiology (efficacy) review(s) (indicate date for each review)	7/17/2008, 4/30/2008
Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
Demographic Worksheet (NME approvals only)	
❖ Statistical review(s) (indicate date for each review)	
❖ Biopharmaceutical review(s) (indicate date for each review)	03/21/2008
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
Clinical studies	11/21/2007
Bioequivalence studies	N/A
❖ CMC review(s) (indicate date for each review)	07/17/2008, 6/24/2008, 3/5/2008
Environmental Assessment	
Categorical Exclusion (indicate review date)	Refer to CMC review
Review & FONSI (indicate date of review)	N/A
Review & Environmental Impact Statement (indicate date of each review)	Refer to CMC Review
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	7/17/2008, 4/30/2008
❖ Facilities inspection (provide EER report)	Date completed: 08/03/2007 (X) Acceptable () Withhold recommendation
Methods validation	(X) Completed () Requested () Not yet requested
Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	02/11/2008, 3/27/2008, 6/19/2008,
Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-156 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Cleviprex
Established Name: Clevidipine IV emulsion
Strengths: (0.5 mg/mL)

Applicant: The Medicines Company
Agent for Applicant (if applicable): NA

Date of Application: July 2, 2007
Date of Receipt: July 2, 2007
Date clock started after UN: NA
Date of Filing Meeting: August 20, 2007
Filing Date: August 31, 2007
Action Goal Date (optional):

User Fee Goal Date: May 2, 2008

Indication requested: _____ when the use of oral therapy is not
feasible or desirable.

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? YES NO

If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES X NO

If no, explain:

- Was form 356h included with an authorized signature? YES X NO
- If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES X NO

If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic X Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats X

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES X NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

- 3. This application is an eCTD NDA. YES X
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO

- Exclusivity requested? YES, _____ Years NO X
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
- If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 65,114

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) March 25, 2003 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) January 30, 2007 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A X YES NO
- Risk Management Plan consulted to OSE/IO? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES X NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team? YES X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 20, 2007

NDA #: 22-156

DRUG NAMES: Cleviprex (clevidipine) 0.5 mg IV emulsion

APPLICANT: The Medicines Company

BACKGROUND: 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 as an oil-in-water emulsion for intravenous administration. The proposed indication is _____, when the use of an oral agent is not feasible or desirable.

The sponsor requested priority review of this application and supports that clevidipine has been designed and developed to address the unmet medical need for improved IV antihypertensive therapy in the treatment of severe and life threatening acute elevations in systemic elevations in systemic blood pressure. The request for a priority review was denied and a letter was sent to the sponsor to notify them of the standard review status.

ATTENDEES: Norman Stockbridge, Abraham Karkowsky, Nhi Beasley, Elizabeth Hausner, Albert DeFelice, Patrick Marroum, Kasturi Srinivasachar, John Lawrence, Christoffer Tornoe, Robert Mello, Ed Fromm

ASSIGNED REVIEWERS:

<u>Discipline/Organization</u>	<u>Reviewer</u>	<u>Proposed Review Date</u>
Medical:	Nhi Beasley, PharmD	February 1, 2008
Secondary Medical:	Abraham Karkowsky, PhD	February 22, 2008
Statistical:	John Lawrence, PhD	February 1, 2008
Pharmacology:	Elizabeth Hausner, PhD	January 18, 2008
Chemistry:	Monica Cooper, PhD	February 1, 2008
Biopharmaceutical:	Lydia Velazquez, PharmD	February 1, 2008
Microbiology, sterility:	Robert Mello, PhD	December 2, 2007
DSI:	Sharon Gershon, PharmD	November 16, 2007
OPS:	Christoffer Tornoe, PhD	December 18, 2007
Regulatory Project Management:	Denise Hinton	March 2, 2008
Other Consults:	DMETS (Darrell Jenkins)/	October 6, 2007
	DDMAC (Lisa Hubbard)	October 6, 2007
	SEALD Team	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? (Consult in DFS) YES NO
If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

		N/A	X	YES	<input type="checkbox"/>	NO	<input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>	
STATISTICS	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>	
BIOPHARMACEUTICS			FILE	X	REFUSE TO FILE	<input type="checkbox"/>	
• Biopharm. study site audits(s) needed?					<input type="checkbox"/>	NO	<input type="checkbox"/>
YES							
PHARMACOLOGY/TOX	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>	
• GLP audit needed?				YES	<input type="checkbox"/>	NO	X
CHEMISTRY			FILE	X	REFUSE TO FILE	<input type="checkbox"/>	
• Establishment(s) ready for inspection?				YES	X	NO	<input type="checkbox"/>
• Sterile product?				YES	X	NO	<input type="checkbox"/>
• If yes, was microbiology consulted for validation of sterilization?				YES	X	NO	<input type="checkbox"/>

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- X Filing issues to be communicated by Day 74. List (optional):
 - is not the correct dosage form nomenclature. This should be replaced by "injectable emulsion" (see USP and Diprivan labeling).
 - The established name should be "clevidipine butyrate" and not "clevidipine" (see USAN).
 - Both the package insert (Description section) and container labels should list the quantitative amounts of all excipients since this is a parenteral product.
 - Provision has been made for room temperature storage of the product for up to 2 months – is this necessary and is the labeling for the storage conditions clear enough to avoid confusion, keeping in mind the photolabile nature of the drug?

ACTION ITEMS:

1. X Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- 4.X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. X Convey document filing issues/no filing issues to applicant by Day 74 (September 14, 2007).

Denise M. Hinton
Regulatory Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Denise Hinton
9/4/2007 04:39:09 PM
CSO

RHPM Overview of NDA 22-156
Cleviprex
(clevidipine butyrate)
0.5mg/mL Injectable Emulsion
June 13, 2008

Sponsor: The Medicines Company
Receipt Date: July 2, 2007
User Fee Goal Date: August 2, 2008
Approval Letter Issued: August 1, 2008

Primary Reviewers

Medical: Bach Nhi Beasley, PharmD
Secondary Medical: Abraham Karkowsky, MD
Statistician: John Lawrence, PhD
Clinical Pharmacologist: Lydia Velazquez, PhD
Pharmacometrics: Christopher Tornoe, PhD
Pharmacologist: Elizabeth Hausner, DVM
Chemist: Monica Cooper, PhD
Microbiologist: Robert Mello, PhD
DSI: Sharon Gershon, PharmD

Background

The Medicines Company submitted a NDA for Cleviprex (clevidipine butyrate) IV emulsion on July 2, 2007 for _____ when the use of an oral agent is not feasible or not desirable. On April 25, 2008 the sponsor submitted a major amendment that included additional pharm/tox and chemistry data. On May 1, 2008, the Division extended the goal date to August 2, 2008 to provide time for a full review of the submission.

Medical/Statistical Joint Review

In their review dated March 10, 2008, Drs Beasley and Lawrence recommended approval of Cleviprex from a clinical and statistical perspective. Regarding efficacy, the results of two adequate, placebo-controlled studies, ESCAPE-1 and ESCAPE-2, for the primary endpoint of bailout to an alternate antihypertensive by 30 minutes, provides substantial evidence that clevidipine is effective in reducing blood pressure in the preoperative setting. Regarding safety, clevidipine has an adverse event profile similar to that of other IV antihypertensives. It was studied directly against sodium nitroprusside, nicardipine and nitroglycerin in three large safety studies called ECLIPSE. The reviewers believe that there is adequate information in the clinical program to assess efficacy and safety, and to write a set of dosing instructions.

Secondary Medical Review

In his review dated May 13, 2008, Dr. Karkowsky supports the approvable recommendation for Cleviprex as a therapy to rapidly decrease blood pressure when oral treatment is not an option. He stated that full approval for clevidipine butyrate is dependant on qualifying three degradants that structurally _____ Should these degradants demonstrate genotoxicity, the specifications for their limits would be substantially lower than what the sponsor currently

NDA 22-156
RHMP Review

Microbiology

In his review dated, April 30, 2008, Dr. Mello recommended an approvable action from a microbiology standpoint. He concluded in the absence of any experimental data, the drug product should be labeled to be used within four (4) hours following the initial penetration of the stopper. Therefore, the sponsor should either provide microbiological data supporting the proposed — holding period following the initial penetration of the stopper or, alternatively, revise the labeling to indicate use within 4 hours following the initial penetration of the stopper.

DSI

In her review dated, November 11, 2007, Dr. Gershon concluded that no significant deviations were noted during the inspection, and no FDA-483 was issued. The data at this site appear valid and DSI recommends the data is acceptable in support of this NDA.

Pediatrics

The pediatric team has concluded that PREA does apply. The pediatric studies will be deferred until August 2011.

Labeling

The sponsor submitted original electronic labeling dated October 1, 2007. After a series of emails and discussions, on August 1, 2008, the sponsor agreed to the final revisions made in labeling for Cleviprex.

Advisory Committee Meeting

No meeting held.

CSO Summary

Based on the recommendations of each reviewer, there are no issues that might prevent an approval on draft action for this NDA.

Alisea Crowley, Pharm.D.

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/s/

Alisea R. Crowley
8/1/2008 03:01:24 PM
CSO

Memo to File

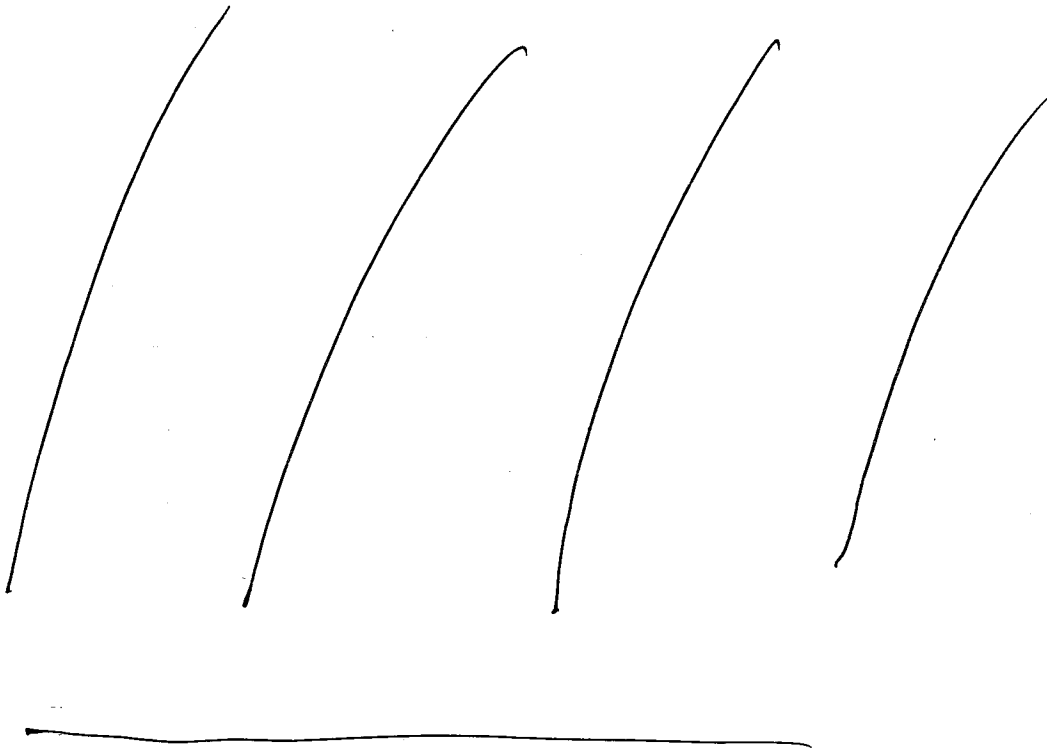
Application: Cleviprex (clevidipine butyrate) Injection
NDA 22-156

Date: July 29, 2008

Subject: Summary of Labeling Teleconference with The Medicines Company

Participants: Robert Temple, MD (ODE1 Office Dir.), Norman Stockbridge, PhD, MD (Dir Div. of Cardiovascular and Renal Drug Products), Monica Cooper, PhD (Chemist), Bach Nhi Beasley, PharmD (Medical Officer), Abraham Karkowsky, MD (Supervisor Medical Officer), Ted Chang (Chemist), Christoffer Tornoe, PhD (Clinical Pharmacologist), Denise Toyer (OSE, Deputy Dir), Kristina Arnwine (Reviewer, OSE), Anne Crandall (Reviewer, OSE), Elizabeth Hausner, PhD (Pharmacologist)

On Monday, July 28, 2008, the Division had a teleconference with The Medicines Company to discuss their proposed package insert, carton and container. The following information is a summary of the discussion and the revisions requested by the Division and OSE.



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 Draft Labeling

 Deliberative Process

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Alisea R. Crowley
7/29/2008 02:59:39 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-156

The Medicines Company
Attention: Lorraine Lucas, Ph.D.
8 Campus Drive
Parsippany, NJ 07054

Dear Dr. Lucas:

Please refer to your July 2, 2007 new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Clevidipine butyrate injectable emulsion 0.5mg/mL.

On April 25, 2008, we received your April 25, 2008 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 2, 2008.

If you have any questions, please call:

Alisea Crowley, Pharm.D.
Regulatory Health Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm

5/1/2008 12:57:33 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-156

DISCIPLINE REVIEW LETTER

The Medicines Company
Attention: Mr. Gregory C. Williams
8 Campus Drive
Parsippany, NJ 07054

Dear Mr. Williams:

Please refer to your July 2, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cleviprex (clevidipine butyrate) Injectable Emulsion, 0.5 mg/mL.

Our reviews of the Pharmacology and Toxicology and Chemistry, Manufacturing and Controls of your submission are complete, and we have identified the following deficiencies:

Pharmacology and Toxicology

- Clevidipine and the major metabolite H152/81 should each be characterized in a receptor screening assay, e.g., a Pan Labs screen of approximately 50 different receptors.
- The genotoxicity of formaldehyde alone and in combination with the other genotoxic substituents of the drug product requires further characterization such as the standard battery of genotoxicity assays.

Chemistry, Manufacturing and Controls

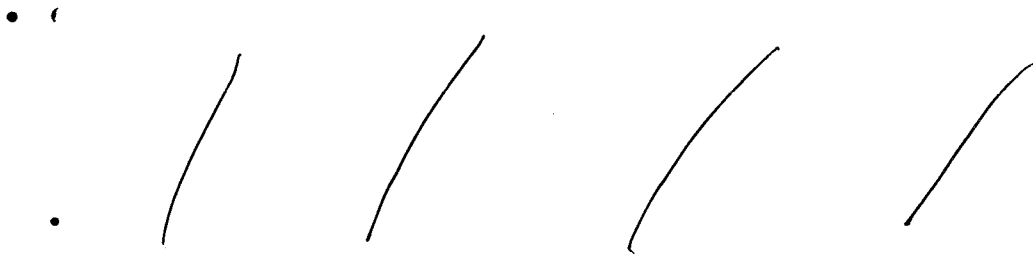
Drug Substance:

- Deficiencies were sent to the DMF holder () the drug substance. Please ensure that the DMF holder responds to these deficiencies promptly.
- **S.4.1 Specifications:**
 - a. List all known impurities separately in the drug substance release and stability specifications.
 - b. Since is a genotoxin and suspected carcinogen, the limit of is not appropriate. The limit should be tightened to a level that gives a maximum daily exposure of no more than the EMEA's Threshold of Toxicological Concern ('day).
 - c. Please justify your proposed limit of for based on safety.
 - d. Please include a test and an acceptance limit for the specific rotation of the drug substance or provide justification based on data for why it is not needed.

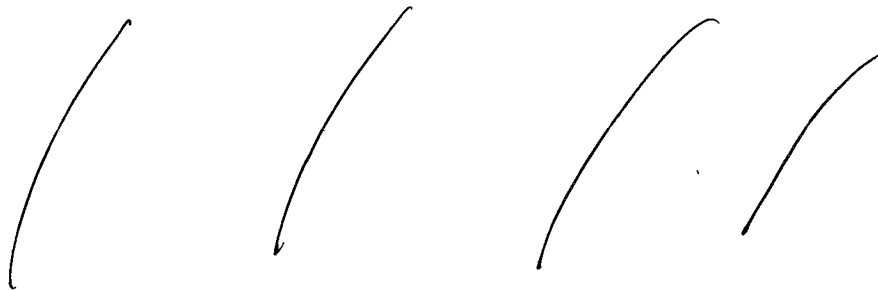
Drug Product:

- Deficiencies were sent to DMF Holder () for the drug product. Please ensure that the DMF Holder responds to these deficiencies promptly.
- **P.5.1 Specification:** Please revise your specification to include a specific identity test for clevidipine butyrate, as your current test by HPLC retention time alone is not specific per ICH Q6A.
- **P.5.1 and P.5.6 Specification:** Please provide a scientific justification for your proposed limits of each for which give structural alerts for genotoxicity. As these limits would be times (per genotoxin) the EMEA's Threshold of Toxicological Concern (TTC), a basic battery of genotoxicity tests should be conducted on these compounds separately and in combination to justify the proposed limits.

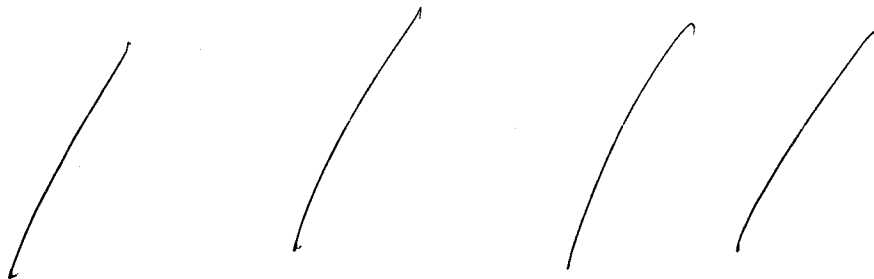
- **P.5.1 and P.5.6 Specification:** The limits for related substances — both specified at NMT — were calculated based on the mean and a range factor of 4.5-fold of the standard deviation. Please use a factor of not more than three (3) for the calculation of range. Moreover, as these two impurities are ; the limits should be tightened as much as possible.
- **P.5.1 and P.5.6 Specification:** The limit for Total Related Substances (proposed NMT was calculated based on the mean and a range factor of 4.5-fold of the standard deviation. Please use a factor of not more than three (3) for the calculation of range.
- **P.8.1 Stability:** Due to the differences between 100-mL and 50-mL bottles — e.g. — the stability data for 100-mL bottles cannot be extrapolated and applied to the 50-mL bottles. The stability data available to date for 50-mL fill size is 12 months, and this does not support a shelf-life. Provide available additional long-term stability data for the 50-ml bottles.
- **P.8.2 Post-Approval Stability Protocol:** The proposed post-approval stability protocol is inadequate for the first three commercial batches. These studies should include long-term and accelerated (up to 6 months) conditions — the same as for the primary batches.



Labeling and Packaging:



We have also evaluated the container labels, carton and insert labeling and have identified the following areas of improvement to minimize potential user error.

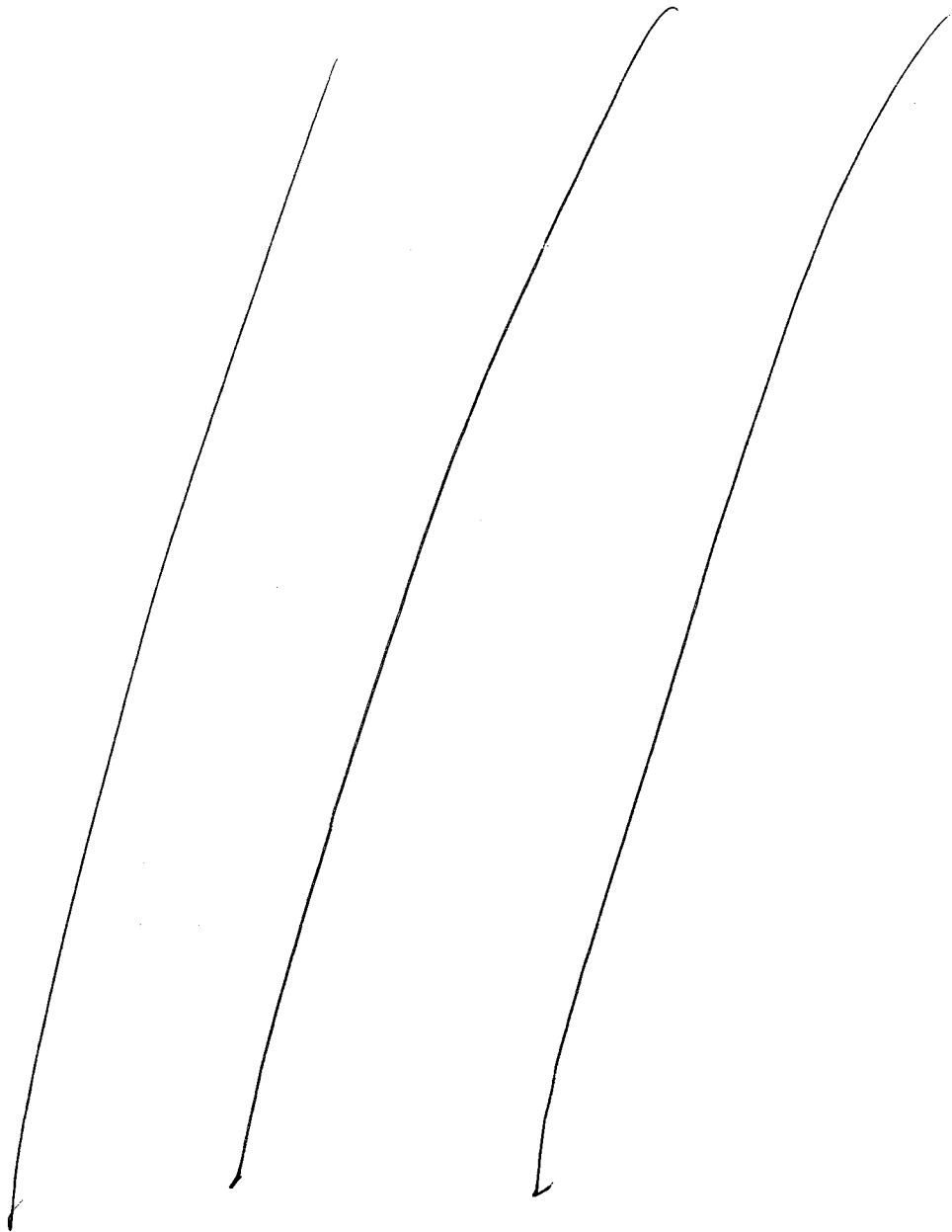


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Draft Labeling

Deliberative Process



We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

NDA 22-156
Cleviprex (clevidipine butyrate) Injectable Emulsion

If you have any questions, please call Denise Hinton, Regulatory Health Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
2/25/2008 05:02:52 PM

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/s/

Denise Hinton

2/4/2008 03:57:37 PM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: November 20, 2007

TO: Denise Hinton
Regulatory Health Project Manager
Nhi Beasley, Pharm.D. Medical Officer (22-156)
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting-Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Sharon K. Gershon, Pharm.D., Regulatory Reviewer

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-156
Sponsor: The Medicines Company

DRUG: Cleviprex (clevidipine IV emulsion) 0.5 mg/mL

CHEMICAL CLASSIFICATION: 1S

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: _____, when the use of oral therapy is not feasible or desirable.

CONSULTATION REQUEST DATE: August 20, 2007

ACTION GOAL DATE: November 21, 2007

PDUFA DATE: January 2, 2008

I. BACKGROUND:

Study Drug: Clevidipine belongs to a well-known class of drugs called dihydropyridine calcium channel antagonists. Clevidipine is the first third generation intravenous dihydropyridine calcium channel blocker that acts by selectively relaxing the smooth muscle cells that line small arteries, resulting in arterial dilation, widening of the artery opening, and without reducing central venous pressure or reducing cardiac output.

Objectives: The primary objective for these two pivotal studies was to determine the efficacy of clevidipine versus placebo in treating preoperative (ESCAPE-1) or postoperative (ESCAPE-2) hypertension, by comparing the incidence of bailout in the clevidipine and placebo treatment groups during the 30-minute time period from initiation of study drug.

ESCAPE-1 Study: This was a multicenter study conducted at 12 study sites in the U.S. The planned sample size was approximately 100 patients. 152 patients were randomized, 105 met post-randomization criteria and 104 were treated. Patients with a recent history of hypertension or who were hypertensive upon admission and who were scheduled for cardiac surgery were eligible for study participation if they were at least 18 years of age, provided written informed consent, and met the following inclusion criteria: 1) met the protocol definition of preoperative hypertension, i.e., systolic blood pressure (SBP) ≥ 160 mmHg after insertion of an arterial line; and 2) the investigator intended to lower the patient's SBP by a minimum of 15% from its baseline value. Duration of treatment was a minimum of 30 minutes, unless bailout occurred, up to a maximum of one hour (or until induction of anesthesia). The primary efficacy endpoint was the incidence of bailout during the 30-minute efficacy evaluation period, defined as the premature and permanent discontinuation of study drug. Adverse events and serious adverse events were assessed until hospital discharge or 7 days, whichever occurred first. Other safety measurements included laboratory values, vital signs, and HR during study drug administration.

ESCAPE-2 Study: This was a multicenter study conducted at 15 study sites in the U.S. The planned sample size was approximately 100 patients. 206 patients were randomized, 110 met post-randomization criteria and were dosed with study medication. Patients who were scheduled for cardiac surgery were eligible for study participation if they were at least 18 years of age, provided written informed consent, and met the following inclusion criteria: 1) expected to survive beyond 24 hour post-surgical procedure; 2) no surgical complications or conditions, present or anticipated, that precluded them from inclusion in a double-blind, placebo-controlled study; 3) the patient met the protocol definition of postoperative hypertension (SBP ≥ 140 mmHg within 4 hours of arrival in a postoperative setting); and 4) the investigator intended to lower the patient's SBP by a minimum of 15% from its baseline value. Duration of treatment was a minimum of 30 minutes, unless bailout occurred, up to a maximum of one hour. The primary efficacy endpoint was the incidence of bailout during the 30-minute efficacy evaluation period, defined as the premature and permanent discontinuation of study drug. Adverse events and serious adverse events were assessed until hospital discharge or 7 days, whichever occurred first. Other safety measurements included laboratory values, vital signs, and HR during study drug administration.

II. RESULTS

Clinical Investigator/Address	No. Subjects	Inspection Dates	Protocol No.	Field Classification	EIR Receipt Date
Harold Minkowitz, M.D. Memorial Hermann – Memorial City Hospital 920 Frostwood Houston, TX 77024 Site 0111	12 subjects enrolled	October 10, 2007	TMC-CLV- 03-01 (ESCAPE-1)	NAI	Nov 9, 2007
Dr. Neil K. Singla, M.D. Huntington Memorial Hospital 100 West Columbia Blvd. Pasadena, CA 91109 Site 0201	20 subjects enrolled	October 3-11, 2007	TMC-CLV- 03-02 (ESCAPE-2)	NAI	Nov 2007

NAI = No deviation from regulations. Data acceptable
 VAI = Minor deviations(s) from regulations. Data acceptable
 VAIr = Deviation(s) from regulations, response requested. Data acceptable
 OAI = Significant deviations for regulations. Data unreliable
 Pending = Inspection not completed

Protocols:

ESCAPE-1 or TMC-CLV-03-01: Efficacy Study of Clevidipine Assessing its Preoperative Antihypertensive Effect in Cardiac Surgery.

ESCAPE-2 or TMC-CLV-03-02: Efficacy Study of Clevidipine Assessing its Postoperative Antihypertensive Effect in Cardiac Surgery.

1. Dr. Harold Minkowitz, Houston, Texas, Site #0111

a. What was Inspected and Scope of Inspection:

Thirteen subjects were screened and 12 subjects were enrolled into this protocol. One subject withdrew their consent before the test article was administered. All study subjects' records were reviewed during the inspection. Case report forms were corroborated with data-listings provided by the sponsor. Adverse events, drug accountability records, and all regulatory records, including sponsor and monitor correspondence, and IRB correspondence were reviewed. The inspection confirmed that all subjects signed an approved informed consent form.

b. Limitations: There were no limitations to this inspection.

c. General Observations: No significant deviations were noted during this inspection, and no FDA-483 was issued.

d. Assessment of Data Integrity: The study appears to have been conducted adequately, and the data at this site appear acceptable to support approval of the NDA.

2. Dr. Neil K. Singla, M.D., Huntington Memorial Hospital, 100 West Columbia Blvd., Pasadena, CA 91109

a. What was inspected: The inspection audited study records from all 20 subjects at this site, including case report forms, source records, laboratory records, adverse events.

b. Limitations: There were no limitations during this inspection.

c. Observations: No significant deviations were noted during this inspection, and no FDA-483 was issued. The field classified this inspection as VAI because of findings of 3 protocol deviations. These deviations were approved by the sponsor following a series of communications by the clinical investigator. The deviations included: lack of reporting segmented and banded neutrophil testing for pre-treatment and follow up hematology tests; using a Troponin I test in stead of CK/MB testing; and rounding the time of dosage administration of study drug to the nearest minute.

The sponsor provided CRFs to the site, and the CRF did not contain a space for recording infusion times in seconds. The sponsor instructed the site to use whole minute intervals when recording on the CRF. The site was consistent in rounding up to a whole number integer on the CRF.

The CK/MB test is an older test to help diagnose if a subject had a heart attack. This hospital used the Troponin I test, and marked "not done" on the CRF for the CK/MB test. The sponsor instructed the site to document it in this way.

The laboratory report documents that neutrophil counts were obtained, but there was no differentiation into bands or segs. There was sufficient documentation that the clinical investigator asked the sponsor how to document the neutrophil count, since their lab does not differentiate the neutrophil value into segs and bands. The sponsor instructed the clinical investigator to ask his lab concerning this issue. The lab responded that only automated neutrophil counts are done, unless there is > 10% bands. If bands are > 10% then a manual count is done.

d. Assessment of Data Integrity: The data at this site appear valid and DSI recommends the data is acceptable in support of this NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

DSI recommends that the data is reliable and can be used in support of this NDA.

{See appended electronic signature page}

**Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations**

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

**Tejashri Purohit-Sheth, M.D.
Acting-Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations**

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/s/

Sharon Gershon
11/21/2007 12:48:46 PM
CSO

Tejashri Purohit-Sheth
11/21/2007 03:27:25 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-156

The Medicines Company
Attention: Gregory C. Williams, Ph.D.
Vice President, Regulatory Affairs and Program Management
8 Campus Drive
Parsippany, NJ 07054

Dear Dr. Williams:

Please refer to your pending new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cleviprex (clevidipine IV emulsion) 0.5 mg/mL.

We also refer to your submissions dated July 25 and August 8, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 31, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Clinical

claims are generally not allowed in labeling

Clinical Pharmacology

Please provide full individual assay analytical method validation reports for each study.

Chemistry

Please amend your labeling as recommended below:

1. ' is not the correct dosage form nomenclature. This should be replaced by "injectable emulsion" (see USP).
2. The established name should be "clevidipine butyrate" and not "clevidipine" (see USAN).
3. Both the package insert (Description section) and container labels should list the quantitative amounts of all excipients since this is a parenteral product.

NDA 22-156

Page 2

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call Commander Denise Hinton, Regulatory Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Norman Stockbridge
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-156

The Medicines Company
Attention: Gregory C. Williams, Ph.D.
Vice President, Regulatory Affairs and Program Management
8 Campus Drive
Parsippany, NJ 07054

Dear Dr. Williams:

Please refer to your pending new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cleviprex (clevidipine IV emulsion) 0.5 mg/mL.

We also refer to our acknowledgment letter dated July 17, 2007, that stated the drug review priority classification for this application would be priority (P).

Our policy regarding determination of priority or standard review status is based on the proposed indication and alternative treatments marketed for the proposed indication. Upon further consideration of your application, we have concluded that this application should receive a standard review. The user fee goal date is May 2, 2007.

Your request for a priority review on the basis that clevidipine IV emulsion would provide "significant improvement compared to marketed products in the treatment... of a disease" and "elimination or substantial reduction of a treatment-limiting drug reaction" as compared to currently marketed products are unsubstantiated. Clevidipine IV emulsion is a dihydropyridine calcium channel blocker, and there are several approved intravenous antihypertensives—including another dihydropyridine calcium channel blocker—that when used appropriately reduce blood pressure effectively and safely. As such, clevidipine does not qualify as satisfying an unmet clinical need.

With respect to providing a significant improvement compared to marketed products, we note that you state that the incidences of death, myocardial infarction, stroke, and renal dysfunction were similar between clevidipine-treated and comparator-treated subjects in the three ECLIPSE studies and you do not report the nominal p-value for this primary endpoint. Only the ECLIPSE-SNP study hints at a nominally significant benefit (mortality) of clevidipine compared to a comparator, but you did not prespecify an alpha *a priori* for this mortality endpoint alone. Furthermore, while the ECLIPSE safety studies compared clevidipine to other approved products, explicit directions on use of the comparator product were not provided to the investigator. As such, the benefit may or may not have been the result of an unfair comparison. For these reasons, your application will receive a standard review.

If you have any questions, please call Denise Hinton, Regulatory Health Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
8/22/2007 01:00:35 PM

DSI CONSULT: Request for Clinical Inspections

Date: August 20, 2007

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCPI, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

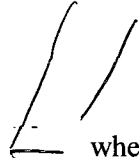
cc: Gary Della'Zanna, D.O, Director, Division of Scientific Investigations, HFD-45

From: Denise Hinton, Regulatory Health Project Manager, HFD-110
Division of Cardiovascular and Renal Products


Subject: **Request for Clinical Site Inspections**
NDA 22-156
The Medicines Company
Cleviprex (clevidipine IV emulsion) 0.5 mg/mL

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site #111 Memorial Hermann- Memorial City Hospital 920 Frostwood Houston, TX 77024	ESCAPE-1 or TMC-CLV- 03-01	13 met prerandomization criteria, 12 met post randomization criteria	 when the use of oral therapy is not feasible or desirable

Request for Clinical Inspections

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site #201 Huntington Memorial Hospital Clinical Management Services 100 West Columbia Blvd Pasadena, CA 91109	ESCAPE-2 or TMC-CLV- 03-02	27 met prerandomization criteria, 20 met post randomization criteria	 when the use of oral therapy is not feasible or desirable

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by November 16, 2007. We intend to issue an action letter on this application by December 21, 2007. The PDUFA due date for this application is January 2, 2008.

Should you require any additional information, please contact Denise Hinton at (301) 796-1090.

Concurrence:

Abraham Karkowsky, MD, Medical Team Leader
 Nhi Beasley, PharmD, Medical Reviewer
 Norman Stockbridge, MD, PhD Division Director (for foreign inspection requests only)

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/s/

Denise Hinton
8/20/2007 07:57:46 AM

Nhi Beasley
8/20/2007 08:42:19 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Office/Division): Lisa Hubbard, RPh, Regulatory Review Officer, DDMAC			FROM (Name, Office/Division, and Phone Number of Requestor): Denise Hinton/DCRP/6-1090		
DATE 6Aug07	IND NO. 65114	NDA NO. 22156	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT 2Jul07	
NAME OF DRUG Clevidipine IV emulsion		PRIORITY CONSIDERATION P	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE 6Oct07	
NAME OF FIRM: The Medicines Company					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE-NDA MEETING	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER			
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END-OF-PHASE 2a MEETING	<input type="checkbox"/> FINAL PRINTED LABELING			
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input type="checkbox"/> LABELING REVISION			
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE			
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> SAFETY / EFFICACY	<input type="checkbox"/> FORMULATIVE REVIEW			
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION	<input type="checkbox"/> PAPER NDA	<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):			
<input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> CONTROL SUPPLEMENT				
II. BIOMETRICS					
<input type="checkbox"/> PRIORITY P NDA REVIEW			<input type="checkbox"/> CHEMISTRY REVIEW		
<input type="checkbox"/> END-OF-PHASE 2 MEETING			<input type="checkbox"/> PHARMACOLOGY		
<input type="checkbox"/> CONTROLLED STUDIES			<input type="checkbox"/> BIOPHARMACEUTICS		
<input type="checkbox"/> PROTOCOL REVIEW			<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):					
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE		
<input type="checkbox"/> BIOAVAILABILITY STUDIES			<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS		
<input type="checkbox"/> PHASE 4 STUDIES			<input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG SAFETY					
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY		
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES			<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE		
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)			<input type="checkbox"/> POISON RISK ANALYSIS		
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP					
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> NONCLINICAL		
COMMENTS / SPECIAL INSTRUCTIONS: Please review the labeling (PI, Carton and Container) for Cleviprex (clevidipine IV emulsion). It is available electronically in the EDR. I will also deliver a hard copy to you today. The DCRP reviewers are to complete their reviews NLT 1Nov07. Thank you.					
SIGNATURE OF REQUESTOR Denise Hinton for Nhi Beasley, Pharm.D.			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

Denise Hinton

8/6/2007 03:48:16 PM

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/s/

Denise Hinton

8/6/2007 02:52:21 PM



NDA 22-156

NDA ACKNOWLEDGMENT

The Medicines Company
Attention: Gregory C. Williams, Ph.D.
Vice President, Regulatory Affairs and Program Management
8 Campus Drive
Parsippany, NJ 07054

Dear Dr. Williams:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cleviprex

Review Priority Classification: Priority (P)

Date of Application: July 2, 2007

Date of Receipt: July 2, 2007

Our Reference Number: NDA 22-156

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 2, 2007 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be January 2, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until insert date. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the

date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Ms. Denise Hinton
Regulatory Health Project Manager
(301) 796-1090

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
7/17/2007 09:01:25 AM

REQUEST FOR CONSULTATION

TO (Office/Division): David Hussong/Jim McVey/Sylvia Gantt
NEW DRUG MICROBIOLOGY STAFF
OC/OO/CDER/OPS/NDMS - HFD-805

FROM (Name, Office/Division, and Phone Number of Requestor): Scott N. Goldie for Kasturi Srinivasachar Division of Pre-Marketing Assessment I, Off. of New Drug Quality Assessment

DATE
July 12, 2007

IND NO.

NDA NO.
22156

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
July 2, 2007

NAME OF DRUG
clavidiopine (clavidiopine IV emulsion)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
2 December 2007

NAME OF FIRM: The Medicines Company

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Microbiology review requested of new NDA application. Please direct questions to Kasturi Srinivasachar at 61760. Submission is in EDR

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Kasturi Srinivasachar
7/16/2007 09:40:34 AM

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

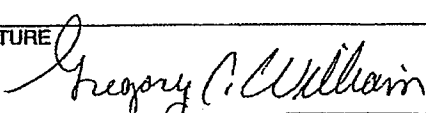
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Gregory Williams, Ph.D	TITLE Vice President, Regulatory Affairs and Program Management
FIRM/ORGANIZATION The Medicines Company, 8 Campus Drive Parsippany NJ 07054	
SIGNATURE 	DATE 07/02/2007

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

12 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

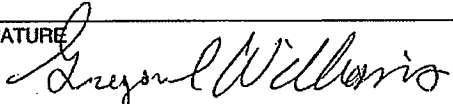
TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated
Name of clinical investigator
as a clinical investigator in the submitted study _____
Name of
_____ is submitted in accordance with 21 CFR part 54. The
clinical study
named individual has participated in financial arrangements or holds financial interests that are
required to be disclosed as follows:

Please mark the applicable check boxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Gregory C Williams, Ph.D.	TITLE Vice President, Regulatory Affairs & Program Management
FIRM/ORGANIZATION The Medicines Company	
SIGNATURE 	DATE 07/02/2007

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

10 Patients enrolled

1 Patient enrolled

Consulting, Sales Support or Educational Programs

Year 2003	\$2,716.00
Year 2004	\$247,233.00
Year 2005	\$295,173.00
Year 2006	\$85,191.00
Year 2007	\$22,926.00
Total	\$653,239.00

Steps taken to minimize bias

_____ enrolled 10 patients in _____ and 1 patient in _____
_____ It is believed that the number of patients (11) enrolled at this site study did not significantly contribute to the overall results & conclusions of the studies.

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/s/

Denise Hinton

7/2/02 03:44:33 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.		
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm		
1. APPLICANT'S NAME AND ADDRESS THE MEDICINES CO Gregory Williams 8 CAMPUS DRIVE Parsippany NJ 07054 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22,156
2. TELEPHONE NUMBER 973-647 6010		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME TBD (clevidipine / clevidipine IV emulsion (0.5 mg/mL))		6. USER FEE I.D. NUMBER PD3007175
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO		
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Gregory Williams</i>		TITLE <i>VP-Reg Affairs and Programs Mgmt</i>
		DATE <i>6/5/07</i>
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$896,200.00		
Form FDA 3397 (12/03)		

Close Print Cover sheet



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,114

The Medicines Company
Attention: Gregory C. Williams, Ph. D.
Vice President, Regulatory Affairs & Program Management
8 Campus Drive
Parsippany, NJ 07054

Dear Dr. Williams:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for (Clevidipine IV emulsion) (0.5 mg/mL).

We also refer to your February 20, 2007, request for fast track designation for _____ when use of an oral agent is not feasible or desirable and for a step-wise rolling submission of sections of a New Drug Application (NDA) under section 506 of the Act.

We have reviewed your request and, for the following reasons, have concluded that your application does not meet the criteria for fast track designation under section 506 of the Act.

In considering Clevidipine IV for Fast Track designation, we are willing to agree that patients with perioperative hypertension (the largest component of your development program) and patients with hypertensive urgencies/emergencies (a relatively smaller component) represent a population with a serious and/or life threatening condition. However, we are not convinced that this represents a population with an unmet medical need as there are other medications that can be administered to treat the condition. In addition, the endpoint you have evaluated in the development program was the effects of clevidipine on blood pressure reduction but not the effects of clevidipine on endpoints such as perioperative ischemia/infarction, bleeding, heart failure, etc. Therefore, our conclusion is that a Fast Track designation is not appropriate for clevidipine in the " _____ when use of oral agent is not feasible or not desirable."

You may wish to review the "Guidance for Industry: Fast Track Drug Development Programs - Designation, Development, and Application Review," located at <http://www.fda.gov/cder/guidance/index.htm>.

Your request for step-wise submission of sections of an NDA is also denied because this program only applies to products with fast track designation. If you submit a new request for fast track designation you may also request step-wise submission of sections of the NDA.

If you have any questions, please call Ms. Denise Hinton, Regulatory Health Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
4/3/2007 12:57:56 PM

IND 65,114

1

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

White Oak
10903 New Hampshire Avenue
Building 22, Room 4156
Silver Spring, MD 20993-0002

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCaRP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (781) 464-1600

Attention: Saraswathy V. Nochur, Ph.D.

Company Name: The Medicine's Company

Phone: (781) 464-1538

Subject: **IND 65,114**
Pre-meeting Comments

Date: March 27, 2006

Pages including this sheet: 9

From: **Denise M. Hinton**
Phone: **301-796-1090**
Fax: **301-796-9841**

**IND 65,114
The Medicines Company
Type B Pre-NDA Meeting
Meeting Minutes**

Sponsor: The Medicine's Company
IND: 65,114
Date of request: November 21, 2006
Date of receipt: November 21, 2006
Date of confirmation: January 27, 2007
Briefing document receipt date: January 2, 2007
Preliminary comments sent: January 25, 2007
Date of meeting: January 30, 2007
Type/Classification: B/Pre-NDA

Division of Cardiovascular and Renal Products:

Norman Stockbridge, MD, PhD	Division Director
Abraham Karkowsky, MD	Team Leader/Medical Officer
Mehul Desai, MD	Medical Officer
Elizabeth Hausner, DVM	Pharmacologist
Patrick Marroum, PhD	Team Leader/Clinical Biopharmaceutist
Denise Hinton	Regulatory Project Manager

The Medicines Company:

Mark Sumeray, MD	Vice President, Clinical Development
Michelle Sumeray, PhD	Senior Director, Program Management
Greg Williams PhD	Vice President, Regulatory Affairs & Program Management
Janet Haymes	Vice President and General Manager (Business Unit)
William Crouthamel, PhD	Vice President, Preclinical Development
Ping Gao, PhD	Vice President, Biostatistics
Tistan Hu, PhD	Director, Biostatistics

Background

The purpose of this meeting is provide the sponsor with feedback with regard to their NDA submission for clevidipine IV emulsion indicated when use of an oral agent is not feasible or desirable.

The Medicines Company proposes to submit their NDA in June 2007.

DISCUSSION

Following introductions, the Sponsor presented slides to support their response to the Division's comments provided in the Preliminary Response Letter dated January 25, 2007. The sponsor stated they would like to further discuss questions 3, 5, and 9 as follows:

GENERAL SUBMISSION

1. The Sponsor proposes to submit the clevidipine NDA in the CTD format. The submission will be a 'hybrid' electronic NDA which will consist of CTD documents in a PDF format

with an electronic table of contents and a defined folder structure (with appropriate bookmarking and hyperlinking but without an XML backbone). It will navigate as an electronic NDA, and will be prepared in accordance with the 1999 guidances, 'Providing Regulatory Submissions in Electronic Format – General Considerations' and 'Providing Regulatory Submissions in Electronic Format - NDAs' as well as the 2001 draft guidance, 'Submitting Marketing Applications According to the ICH-CTD format – General Considerations'. Is this approach acceptable to the Division?

Preliminary Response

Yes, the approach is acceptable. Please clarify that the CTD documents in a PDF format will be “searchable” and will allow the reviewer to copy text and tables.

Discussion during Face to Face Meeting

The sponsor agreed with the above comments.

2. The Sponsor will provide electronic SAS datasets for each individual study according to the 1999 guidance 'Providing Regulatory Submissions in Electronic Format - NDAs'. Therefore, TMC proposes that subject line listings will not be submitted in the application nor will traditional subject profiles. Does the Division agree with this approach?

Preliminary Response

Yes, the approach is acceptable.

Discussion during Face to Face Meeting

The sponsor agreed with the above comments.

CLINICAL

3. TMC refers to the meeting held with the Division on March 15, 2006 during which the potential indication statement for clevidipine was discussed.

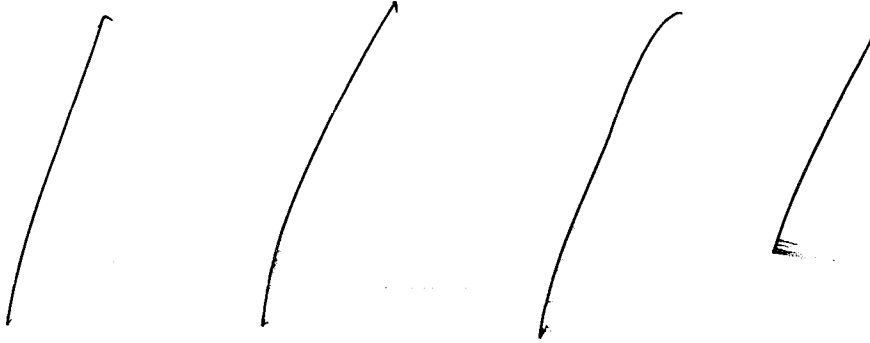
At the conclusion of the current clinical development program for clevidipine, over 2000 subjects will have been studied and over 1000 will have been treated with clevidipine. The program consists of four Phase I studies in healthy subjects, nine Phase II and III efficacy and safety studies of patients with essential hypertension and perioperative hypertension undergoing cardiac surgery, a Phase II PK/PD and safety study of patients with essential hypertension treated with prolonged continuous infusion, and a Phase III efficacy and safety study of patients with severe hypertension. Given the successful completion of the above program, does the Division agree that the data would be adequate to support the following indication statement:

'Clevidipine IV emulsion is indicated for _____
_____ when use of an oral agent is not feasible or not desirable?'

Preliminary Response

The label would be dependent on the data. Whether the INDICATION would refer to
would
likely be dependent on the data.

Discussion during Face to Face Meeting



4. Based on data generated from the clinical program described above, the Sponsor has identified key claims for clevidipine. Assuming that the data are supportive, does the Division agree that the claims are appropriate?

Preliminary Response

This is a review issue. We will also consult DDMAC for advice on some of the claims included within your description.

Discussion during Face to Face Meeting

The sponsor agreed with the above comments.

5. The FDA guidance documents entitled, 'Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study design, Data Analysis, and Impact on Dosing and Labeling' and 'Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function - Study Design, Data Analysis, and Impact on Dosing and Labeling' specify that certain criteria determine the need for a drug to be studied in patients with renal or hepatic dysfunction. Since the metabolism and elimination of clevidipine is independent of hepatic and renal function and that clevidipine is hydrolyzed by plasma and tissue esterases to a pharmacologically inactive carboxylic acid metabolite (M1 – H152/81), the Sponsor has not conducted specific PK studies in special populations with various degrees of underlying hepatic and renal impairment. Does the Division concur with the Sponsor's view that such studies are unnecessary for clevidipine?

Preliminary Response

No, the Division does not concur with your view that the studies stated above are not necessary for clevidipine. Based on the information provided in the background document, clevidipine inhibits a number of isoenzymes. We need to know what happens to M1 and the

pharmacological activity of M1. You might also need to address the potential for drug-drug interaction with clevidipine.

Discussion during Face to Face Meeting

The Sponsor believes they have sufficient data available to address these issues and that additional studies are not required as stated in previous meetings with the Agency in August 2003 and July 2004. They presented an overview of the human metabolic pathway and provided additional background information to support their argument.

The Division stated that if the Sponsor intends that the drug would be used long-term, then they would need to perform drug-drug interaction studies. If the drug will not be used as long-term treatment, then no additional PK studies or drug-drug interaction studies are required.

6. The Sponsor has conducted PK/PD analyses demonstrating that clearance of clevidipine is independent of body weight. During previous discussions with the Division (September 10, 1997), a non weight-based dosing approach was discussed. The Division agreed that the available PK data suggested that such an approach might be justified. Subsequently, TMC has conducted a PK/PD study in patients with essential hypertension and a Phase III study in patients with severe hypertension (VELOCITY) using a non weight-based fixed starting dose, with titration to effect (VELOCITY) or forced titration (PK/PD study). The Sponsor believes that the available information supports a fixed starting dose approach with dose titration to desired blood pressure response, and that this dosing regimen will be included in the 'Dosage and Administration' section of the prescribing information. Assuming that the data are supportive, does the Division agree with this approach?

Preliminary Response

The Division agrees that the dose should be independent of body weight.

Discussion during Face to Face Meeting

The sponsor agreed with the above comments.

7. The Sponsor conducted a thorough QT/QTc clinical study in consideration of the ICH E14 guidance, the design of which included input from the Division (given during a meeting held on December 14, 2004) and from Dr. Mehul Desai (given during a teleconference on April 17, 2006). The Sponsor concluded that the study successfully demonstrated the absence of a prolongation effect of clevidipine on the duration of cardiac repolarization. Does the Division agree that the study has adequately addressed their request for additional clinical data?

Preliminary Response

The results from the clinical QT study you have conducted in healthy volunteers most notably showed that clevidipine, at the doses evaluated, produced marked increases in heart rate. Such marked increases in heart rate, even when corrected for using various formulae,

confound the interpretability of a drug-induced cardiac repolarization effect. We expect to utilize the totality of data collected during the clevidipine development program to make an overall benefit/risk assessment.

Discussion during Face to Face Meeting

The sponsor agreed with the above comments.

8. The Sponsor has identified analyses to be performed on the integrated safety and efficacy data, as described in the relevant statistical analysis plans. Does the Division agree with the proposed approach for the integrated evaluation of the safety and efficacy of clevidipine?

Preliminary Response

The Division agrees with the approach for the integrated evaluation of safety and efficacy.

Discussion during Face to Face Meeting

The sponsor agreed with the above comments.

CMC (QUALITY)

9. Clevidipine emulsion is a sterile, parenteral, oil in water emulsion which contains the active ingredient clevidipine and the following excipients: soybean oil, glycerin, purified egg yolk phospholipids and sodium hydroxide.

The physical stability of the emulsion and the chemical stability of the active ingredient, clevidipine, are assured by assessing routine parameters including appearance, particle size distribution, pH, clevidipine concentration and degradation products.

The identification and concentration of the excipients in the finished drug product have also been tested on release and on stability throughout the development of the clevidipine emulsion. Since it is not usual practice to test excipient concentration in the finished drug product, and because all results have met the acceptance criteria upon release and remain unchanged throughout stability, the Sponsor believes that continued measurement of the excipients is not required.

Therefore, the Sponsor proposes to discontinue testing of the excipients (soybean oil, glycerin, purified egg yolk phospholipids) and these parameters will not be included in the finished product release specification for commercial batches of clevidipine emulsion. Does the Division agree with this approach?

Preliminary Response

The Division does not agree with this approach and recommends continuation of excipient testing for product release since these excipients

The sponsor has not provided adequate information in regards to the test methods used for quantitation of the excipients and their suitability for the intended purpose.

Discussion during Face to Face Meeting/Teleconference

The Sponsor agreed to continue excipient testing for product release and to provide the requested information in the NDA.

Additional comments:

PK-PD Model:

The submission should include an adequate PK-PD model of each of the studies or at least for the studies with larger numbers of subjects and longer durations of infusion times. The parameters of interest for modeling relative to concentrations or doses are DBP, SBP and heart rate. We are interested in whether there is substantial hysteresis particularly at longer durations of infusions. We are also interested in the effect upon transition to other treatments.

Discussion during Face to Face Meeting

The Division agreed, providing that the data in the NDA are supportive, that the following PK-PD analyses are sufficient as proposed by the sponsor:

- PK-PD study (72hour continuous infusion in patients)
 - mild/moderate chronic hypertension
 - 52 patients, 4 dosing cohorts (10 Clevidipine, 3 placebo)
 - 2, 4, 8, 16 mg/h forced titration
 - Hemodynamics (DBP/SBP and heart rate)
 - Evaluating rebound, hysteresis and tolerance
 - Safety

SAD-0018 (up to 24 hour continuous infusion)

- 14 healthy volunteers
- 0.9 to 3.2 µg/kg/min
- PK sampling at steady state and end of infusion
- Hemodynamics (DBP/SBP and heart rate)
- Evaluating rebound and hysteresis
- Safety

Safety:

The Division recommends that you explore the consequences of any use of beta blockade to control the clevidipine-provoked tachycardia.

Discussion during Face to Face Meeting

Dr. Karkowsky referred to the fenoldopam drug product and explained that it was previously found to promote tachycardia. The tachycardia was then treated with a beta-blocker resulting in further decreased blood pressure. He recommended that the Sponsor explore the consequences of any use of a beta blockade to control the clevidipine-provoked tachycardia to address safety, as it is not an efficacy issue.

The Sponsor presented slides and a brief overview of their experience with reflex tachycardia and beta-blockers. They stated that concomitant beta-blocker use has not been a problem and that beta-blockers are more likely as a replacement therapy than concomitant therapy. Safety data addressing these issues are available in the severe hypertension study and will be addressed in the summary of clinical safety upon submission of the NDA.

The Division agreed that providing that the data in the NDA are supportive, the Sponsor's approach is sufficient to address safety.

Pediatrics:

No pediatric studies have been submitted. We remind you that a waiver has not been granted for pediatric studies.

Discussion during Face to Face Meeting

The Sponsor agreed to submit an application for deferral prior to submitting the NDA. The Division agrees to grant a deferral, however, a basic outline for pediatric study plans should be in place by the time the drug is approved.

Metabolites:

Clevidipine has a single chiral center. Some information is needed on the fate of each of the clevidipine optical isomers as well as the activity profile for each of these optical isomers.

Although clevidipine is rapidly metabolized, the sites and time for the ultimate excretion of M1 and other metabolites should be addressed. Please provide justification for why you believe M1 is "pharmacologically inactive."

Discussion during Face to Face Meeting

After a brief discussion and clarification from the sponsor with regard to the data addressing the above issues, the Division agreed that sufficient data are available to address the concerns presented in the preliminary comments. Additional studies are not required.

Non-Clinical

1. Genotoxicity

The reverse bacterial mutation assay was repeated using formaldehyde dehydrogenase (FDH) on the premise that this would decrease the mean number of revertants generated. Data for a formaldehyde control was not found in the study report. The results of the assay do not show a decrease in mean revertants in the presence of FDH, therefore not supporting the original premise.

Discussion during Face to Face Meeting

The Sponsor agrees with the Division's comments with regard to genotoxicity in the two previously conducted studies. As presented in the attached slides, the Sponsor has conducted a third study which addresses the Division's concerns and contains the appropriate FDH controls confirming that formaldehyde was responsible for previous positive results in-vitro. This information will be included in the NDA.

Based on the Sponsor's presentation and provided that the data in the NDA are supportive, the Division agrees there will be sufficient information to address the Division's concerns.

2. Testicular toxicity

The methods of evaluation used contain a great deal of variability, making the overall assessment difficult. The Division does not agree that the data as presented supports the conclusion of no drug effect upon the male reproductive tract.

Discussion during Face to Face Meeting

As presented in their slides, the Sponsor agrees with the Division's comments which are consistent with the 14-day beagle dog chronic safety study, however believes that this does not constitute a safety issue as sufficient data are available to assess male reproductive tract safety. The Sponsor then summarized their studies supporting male reproductive tract safety.

The Division (Dr. Hausner) stated that there were some histological effects in the recent dog study and that this is consistent with some calcium channel blockers being labeled as having an unknown effect on male fertility. It was stated that the short duration of exposure to clevidipine should be considered. The Sponsor was asked

The Division stated we would have further discussions with regard to the labeling upon complete review of the application.

approval issue and no additional studies are required. This is not an

Additional Discussion:

Fast Track versus Priority Review

The Sponsor stated they are considering the submission of their application for Fast Track status on the basis of clevidipine addressing a currently unmet need and providing a significant medical advantage over existing therapies. They are also interested in a rolling submission. They briefly mentioned clevidipine's advantage over sodium nitroprusside and nicardipine.

The Division stated that a Priority Review could be considered in lieu of Fast Track, as the Sponsor has completed their Phase 3 program. The Sponsor was asked to provide arguments against all approved alternative treatments including nicardipine and fenoldopam and the Division will consider the written request.

Meeting Recorder: {See appended electronic signature page}
Denise M. Hinton

Chair Concurrence: {See appended electronic signature page}
Norman Stockbridge, MD, PhD

Draft:2/16/07

Final:3/01/07

RD:

Hausner 2/28/07

Marroum 2/28/07

Desai 3/1/07

Karkowsky3/1/07

Stockbridge 3/1/07

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

/s/

Denise Hinton
3/1/2007 02:24:03 PM

Norman Stockbridge
3/1/2007 03:58:01 PM

**APPEARS THIS WAY
ON ORIGINAL**

**IND 65,114
The Medicines Company
Type B Pre-NDA Meeting
Preliminary Responses**

"This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 30, 2007 from 1:00-2:30 PM between The Medicines Company and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting by contacting the Regulatory Project Manager, but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principle questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to your development plan, the purpose of the meeting, and/or to the questions based on our responses herein, we may not be able to reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting."

DISCUSSION

GENERAL SUBMISSION

1. The Sponsor proposes to submit the clevidipine NDA in the CTD format. The submission will be a 'hybrid' electronic NDA which will consist of CTD documents in a PDF format with an electronic table of contents and a defined folder structure (with appropriate bookmarking and hyperlinking but without an XML backbone). It will navigate as an electronic NDA, and will be prepared in accordance with the 1999 guidances, 'Providing Regulatory Submissions in Electronic Format – General Considerations' and 'Providing Regulatory Submissions in Electronic Format - NDAs' as well as the 2001 draft guidance, 'Submitting Marketing Applications According to the ICH-CTD format – General Considerations'. Is this approach acceptable to the Division?

Preliminary Response

Yes, the approach is acceptable. Please clarify that the CTD documents in a PDF format will be "searchable" and will allow the reviewer to copy text and tables.

2. The Sponsor will provide electronic SAS datasets for each individual study according to the 1999 guidance 'Providing Regulatory Submissions in Electronic Format - NDAs'. Therefore, TMC proposes that subject line listings will not be submitted in the application nor will traditional subject profiles. Does the Division agree with this approach?

Preliminary Response

Yes, the approach is acceptable.

CLINICAL

3. TMC refers to the meeting held with the Division on March 15, 2006 during which the potential indication statement for clevidipine was discussed.

At the conclusion of the current clinical development program for clevidipine, over 2000 subjects will have been studied and over 1000 will have been treated with clevidipine. The program consists of four Phase I studies in healthy subjects, nine Phase II and III efficacy and safety studies of patients with essential hypertension and perioperative hypertension undergoing cardiac surgery, a Phase II PK/PD and safety study of patients with essential hypertension treated with prolonged continuous infusion, and a Phase III efficacy and safety study of patients with severe hypertension. Given the successful completion of the above program, does the Division agree that the data would be adequate to support the following indication statement:

'Clevidipine IV emulsion is indicated _____
_____ when use of an oral agent is not feasible or not desirable?'

Preliminary Response

The label would be dependent on the data. Whether the INDICATION would refer to _____ would likely be dependent on the data.

4. Based on data generated from the clinical program described above, the Sponsor has identified key claims for clevidipine. Assuming that the data are supportive, does the Division agree that the claims are appropriate?

Preliminary Response

This is a review issue. We will also consult DDMAC for advice on some of the claims included within your description.

5. The FDA guidance documents entitled, 'Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study design, Data Analysis, and Impact on Dosing and Labeling' and 'Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function - Study Design, Data Analysis, and Impact on Dosing and Labeling' specify that certain criteria determine the need for a drug to be studied in

patients with renal or hepatic dysfunction. Since the metabolism and elimination of clevidipine is independent of hepatic and renal function and that clevidipine is hydrolyzed by plasma and tissue esterases to a pharmacologically inactive carboxylic acid metabolite (M1 – H152/81), the Sponsor has not conducted specific PK studies in special populations with various degrees of underlying hepatic and renal impairment. Does the Division concur with the Sponsor's view that such studies are unnecessary for clevidipine?

Preliminary Response

No, the Division does not concur with your view that the studies stated above are not necessary for clevidipine. Based on the information provided in the background document, clevidipine inhibits a number of isoenzymes. We need to know what happens to M1 and the pharmacological activity of M1. You might also need to address the potential for drug-drug interaction with clevidipine.

6. The Sponsor has conducted PK/PD analyses demonstrating that clearance of clevidipine is independent of body weight. During previous discussions with the Division (September 10, 1997), a non weight-based dosing approach was discussed. The Division agreed that the available PK data suggested that such an approach might be justified. Subsequently, TMC has conducted a PK/PD study in patients with essential hypertension and a Phase III study in patients with severe hypertension (VELOCITY) using a non weight-based fixed starting dose, with titration to effect (VELOCITY) or forced titration (PK/PD study). The Sponsor believes that the available information supports a fixed starting dose approach with dose titration to desired blood pressure response, and that this dosing regimen will be included in the 'Dosage and Administration' section of the prescribing information. Assuming that the data are supportive, does the Division agree with this approach?

Preliminary Response

The Division agrees that the dose should be independent of body weight.

7. The Sponsor conducted a thorough QT/QTc clinical study in consideration of the ICH E14 guidance, the design of which included input from the Division (given during a meeting held on December 14, 2004) and from Dr. Mehul Desai (given during a teleconference on April 17, 2006). The Sponsor concluded that the study successfully demonstrated the absence of a prolongation effect of clevidipine on the duration of cardiac repolarization. Does the Division agree that the study has adequately addressed their request for additional clinical data?

Preliminary Response

The results from the clinical QT study you have conducted in healthy volunteers most notably showed that clevidipine, at the doses evaluated, produced marked increases in heart rate. Such marked increases in heart rate, even when corrected for using various formulae, confound the interpretability of a drug-induced cardiac repolarization effect.

We expect to utilize the totality of data collected during the clevidipine development program to make an overall benefit/risk assessment.

8. The Sponsor has identified analyses to be performed on the integrated safety and efficacy data, as described in the relevant statistical analysis plans. Does the Division agree with the proposed approach for the integrated evaluation of the safety and efficacy of clevidipine?

Preliminary Response

The Division agrees with the approach for the integrated evaluation of safety and efficacy.

CMC (QUALITY)

9. Clevidipine emulsion is a sterile, parenteral, oil in water emulsion which contains the active ingredient clevidipine and the following excipients: soybean oil, glycerin, purified egg yolk phospholipids and sodium hydroxide.

The physical stability of the emulsion and the chemical stability of the active ingredient, clevidipine, are assured by assessing routine parameters including appearance, particle size distribution, pH, clevidipine concentration and degradation products.

The identification and concentration of the excipients in the finished drug product have also been tested on release and on stability throughout the development of the clevidipine emulsion. Since it is not usual practice to test excipient concentration in the finished drug product, and because all results have met the acceptance criteria upon release and remain unchanged throughout stability, the Sponsor believes that continued measurement of the excipients is not required.

Therefore, the Sponsor proposes to discontinue testing of the excipients (soybean oil, glycerin, purified egg yolk phospholipids) and these parameters will not be included in the finished product release specification for commercial batches of clevidipine emulsion. Does the Division agree with this approach?

Preliminary Response

The Division does not agree with this approach and recommends continuation of excipient testing for product release since these excipients

_____ Adequate information in regards to the test methods used for quantitation of the excipients and their suitability for the intended purpose should be provided.

Additional comments:

The submission should include an adequate PK-PD model of each of the studies or at least for the studies with larger numbers of subjects and longer durations of infusion times. The parameters of interest for modeling relative to concentrations or doses are DBP, SBP and heart rate. We are interested in whether there is substantial hysteresis particularly at longer durations of infusions. We are also interested in the effect upon transition to other treatments.

Safety:

The Division recommends that you explore the consequences of any use of beta blockade to control the clevidipine-provoked tachycardia.

Pediatrics:

No pediatric studies have been submitted. We remind you that a waiver has not been granted for pediatric studies.

Metabolites:

Clevidipine has a single chiral center. Some information is needed on the fate of each of the clevidipine optical isomers as well as the activity profile for each of these optical isomers.

Although clevidipine is rapidly metabolized, the sites and time for the ultimate excretion of M1 and other metabolites should be addressed. Please provide justification for why you believe M1 is "pharmacologically inactive."

Non-Clinical

1. Genotoxicity

The reverse bacterial mutation assay was repeated using formaldehyde dehydrogenase (FDH) on the premise that this would decrease the mean number of revertants generated. Data for a formaldehyde control was not found in the study report. The results of the assay do not show a decrease in mean revertants in the presence of FDH, therefore not supporting the original premise.

2. Testicular toxicity

The methods of evaluation used contain a great deal of variability, making the overall assessment difficult. The Division does not agree that the data as presented supports the conclusion of no drug effect upon the male reproductive tract.

If you have any questions, please call CDR Denise Hinton, Regulatory Project Manager, at (301) 796-1090.

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this page is the manifestation of the electronic signature.**

/s/

Abraham Karkowsky
1/26/2007 02:56:19 PM
For N. Stockbridge.

Teleconference between The Medicines Company and the FDA

Sponsor: The Medicine's Company
IND: 65,114
Date of request: January 16, 2006
Date of receipt: January 17, 2006
Date of confirmation: January 27, 2006
Date of teleconference: March 15, 2006
Time: 10:00 AM – 11:30 AM
Type/Classification: C/Guidance with regard to a new indications statement

FDA Participants:

Norman Stockbridge, MD, PhD Acting Director,
Division of Cardiovascular and Renal Products
Thomas Marciniak, MD Medical Team Leader,
Division of Cardiovascular and Renal Products
Mehul Desai, MD Medical Officer,
Division of Cardiovascular and Renal Products
Lydia Velazquez, PharmD Clinical Pharmacologist and Biopharmaceutist
Division of Clinical Pharmacology and Biopharmaceutics 1
Denise M. Hinton Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

The Medicines Company Participants:

Mark Sumeray, MD VP, Clinical Development
Sara Nochur, PhD Sr. Director, Regulatory Affairs
Janet Haymes Head, Business Unit
James Wong, PhD Director, Clinical Pharmacology
William Crouthamel, PhD VP, Preclinical Development
Malcolm Lloyd, MD Sr. Director, Medical Affairs
Brian Leuthner Director, Marketing
Linda Rootkin Director of Clinical Operations

Background:

The Division provided preliminary comments to The Medicines Company request for a Type C meeting to discuss the clinical data requirements to support the proposed revised indication statement for clevidipine. The Sponsor requested that the indication statement be revised from _____ to _____ when oral therapy is not feasible or desirable".

Discussion:

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

IND 65,114

5

Meeting recorder: *{See appended electronic signature page}*

Denise M. Hinton

Meeting concurrence: *{See appended electronic signature page}*

Norman Stockbridge, Ph.D.

Draft: 20Mar06

Final: 27Mar06

RD:

Velazquez 3/22/2006

Desai 3/23/2006

Marciniak 3/23/2006

Stockbridge 3/26/06

Preliminary Response

Sponsor: The Medicine's Company
IND: 65,114
Date of briefing document: February 27, 2006

Date of internal pre-meeting: March 8, 2006
Type/Classification: C/Guidance with regard to a new indications statement

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D.	Medical Team Leader, Division of Cardiovascular and Renal Products
Mehul Desai, M.D.	Medical Officer, Division of Cardiovascular and Renal Products
Lydia Velazquez Pharm.D.	Clinical Pharmacologist and Biopharmaceutist Division of Clinical Pharmacology and Biopharmaceutics 1
Denise M. Hinton	Regulatory Health Project Manager Division of Cardiovascular and Renal Products

This material consists of our preliminary responses to your questions and any additional comments in preparation for the teleconference scheduled for March 15, 2006 from 10:00 - 11:30 AM EST between The Medicines Company and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to your development plan, the purpose of the meeting or to the questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

Purpose of the Meeting:

The Medicines Company requested this meeting to establish the clinical data requirements to support the proposed revised indication statement for clevidipine.

Questions:

1. Upon successful completion of the clevidipine Phase 3 program comprising a total of approximately 1700 patients undergoing cardiac surgery, together with the additional PK/PD and safety study in patients with essential mild to moderate hypertension and dosing safety study in patients with severe hypertension, would the overall clinical program be adequate to support the following label for clevidipine ' when oral therapy is not feasible or not desirable?'

Response:

Four handwritten checkmarks (✓) indicating a positive response to the question.

2. Are the study designs as proposed acceptable for the revised indication?

Five handwritten checkmarks (✓) indicating a positive response to the question.

We also note that there are other outstanding issues from the development program that must be addressed in the NDA submission. The following are some of the issues that are outstanding:

- Enantiomer activity and how it relates to safety and efficacy must be addressed as discussed at the March 2003 meeting.
- Whether and where formaldehyde accumulates during treatment must be determined as discussed at the March 2003 and July 2004 meetings.

IND 65,114

8

- The effects of clevidipine upon the QTc interval must be evaluated as discussed at the July 2004 meeting and December 2004 teleconference.

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.

Director

Division of Cardiovascular and Renal Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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/s/

Norman Stockbridge

3/9/2006 03:32:05 PM

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this page is the manifestation of the electronic signature.**

/s/

Denise Hinton
3/27/2006 11:17:39 AM

Norman Stockbridge
3/27/2006 01:02:03 PM

Resnick, Charles A

From: Hinton, Denise
Sent: Monday, March 13, 2006 10:57 AM
To: Stockbridge, Norman L; Marciniak, Thomas; Desai, Mehul; Velazquez, Lydia V; Marroum, Patrick J; Resnick, Charles A
Subject: FW: Additional information on clevidipine; The Medicines Company
Attachments: SAD-0010 Report The pharmacokinetics and pharmacodynamics of clevi.pdf; Report No. 1317.pdf; SAD-0018 Clinical Study Report.pdf

Please review the attached documents prior to the teleconference scheduled for 15Mar06. The pre-meeting is scheduled from 0900-1000.

Thanks,

Denise

From: Sara Nochur [mailto:Sara.Nochur@THEMEDCO.com]
To: Hinton, Denise
Subject: Additional information on clevidipine; The Medicines Company

Dear Denise,

We plan to address the outstanding issues from the development program that have been identified by the Agency (in your facsimile dated March 9, 2006) in the NDA submission. However, in order to provide complete information in preparation for the meeting next week, please see our responses to these issues (outside of the two questions we had asked in the background package, IND Serial # 047 dated February 27, 2006). The study reports attached here have all been submitted to FDA previously.

- Demonstration of the efficacy and safety of the enantiomers: Both enantiomers are present in the clevidipine drug product in equal amounts. We have data from a clinical study in patients with essential hypertension (SAD-0010, attached below) which demonstrates that the concentration response of the two enantiomers are virtually identical and are similar to that of clevidipine. Clevidipine was safe in this study and the formulation of clevidipine used in all clinical studies remains the same.

We also have a study in rats that demonstrates that both enantiomers have the same efficacy in lowering blood pressure (Study 1317, attached below).

<<SAD-0010 Report The pharmacokinetics and pharmacodynamics of clevi.pdf>> <<Report No. 1317.pdf>>

- Whether and where formaldehyde accumulates: In the March 25, 2003 meeting, the Agency had suggested a clinical study to determine this; however, in the July 18, 2004 meeting, we agreed with the Agency's recommendation to conduct a study in rats with radiolabeled clevidipine. This study has been completed. A copy of the final study report was submitted to the Agency along with the 2005 Annual Report (IND Serial # 041 dated August 22, 2005). *Report of the rat vcc distribution study does not mention formaldehyde.*
- The effects of clevidipine on QTc: We are planning on completing a QTc study prior to NDA submission; the study report will be included with the NDA.
- PK/PD modeling: Two clinical studies with clevidipine elucidate its PK/PD effects. One is in healthy volunteers (SAD-0018, attached below) when clevidipine was dosed for a short duration (20 min) and for a long duration (24 h); the other is in patients with essential hypertension (SAD-0010, attached above) in which clevidipine was dosed for 4 h including a 2-h titration period followed by a 2-h dosing period at the fixed dose (4 dosing regimens were assessed). Onset and offset of effect as well as hysteresis have been evaluated and the data also include a PK/PD model. The current proposed PK/PD study (synopsis sent with our recent background package - IND Serial # 047 dated February 27, 2006) addresses even longer durations of dosing (up to 72 h) as well as assessment of tolerance, rebound. We will include PK assessments to ensure adequate capture of PK along with the PD effects.

<<SAD-0018 Clinical Study Report.pdf>>

I hope these help address the issues raised. We would appreciate it if you could forward this to the appropriate reviewers so that they are aware of the significant amount of data that we already have.

I will send hard copies (the usual original and 2 copies to the Central Document Room, please let me know if that is not adequate) of this to you early next week.

For the teleconference, please use the following call-in #: 866-836-0844; participant code: 904916. If you have trouble dialing in, please call me on my cell phone at 617-967-1742.

Thanks.

Sincerely,
Sara

Sara Nochur, Ph.D.
Sr. Director, Regulatory Affairs
The Medicines Company
200 Fifth Avenue, Waltham, MA 02451
Tel.: 781-464-1538
Fax: 781-464-1600

Preliminary Response

Sponsor: The Medicine's Company
IND: 65,114
Date of briefing document: February 27, 2006

Date of internal pre-meeting: March 8, 2006
Type/Classification: C/Guidance with regard to a new indications statement

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D.	Medical Team Leader, Division of Cardiovascular and Renal Products
Mehul Desai, M.D.	Medical Officer, Division of Cardiovascular and Renal Products
Lydia Velazquez Pharm.D.	Clinical Pharmacologist and Biopharmaceutist Division of Clinical Pharmacology and Biopharmaceutics 1
Denise M. Hinton	Regulatory Health Project Manager Division of Cardiovascular and Renal Products

This material consists of our preliminary responses to your questions and any additional comments in preparation for the teleconference scheduled for March 15, 2006 from 10:00 - 11:30 AM EST between The Medicines Company and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to your development plan, the purpose of the meeting or to the questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

Purpose of the Meeting:

The Medicines Company requested this meeting to establish the clinical data requirements to support the proposed revised indication statement for clevidipine.

Questions:

1. Upon successful completion of the clevidipine Phase 3 program comprising a total of approximately 1700 patients undergoing cardiac surgery, together with the additional PK/PD and safety study in patients with essential mild to moderate hypertension and dosing safety study in patients with severe hypertension, would the overall clinical program be adequate to support the following label for clevidipine _____ when oral therapy is not feasible or not desirable?"

Response:

2. Are the study designs as proposed acceptable for the revised indication?

We also note that there are other outstanding issues from the development program that must be addressed in the NDA submission. The following are some of the issues that are outstanding:

- Enantiomer activity and how it relates to safety and efficacy must be addressed as discussed at the March 2003 meeting.

- Whether and where formaldehyde accumulates during treatment must be determined as discussed at the March 2003 and July 2004 meetings.
- The effects of clevidipine upon the QTc interval must be evaluated as discussed at the July 2004 meeting and December 2004 teleconference.

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.

Director

Division of Cardiovascular and Renal Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
3/9/2006 03:32:05 PM

Minutes of a meeting between The Medicines Company and the Division of Cardio-Renal Drug Products

Sponsor: The Medicines Company
IND: 65,114
Date of request: November 24, 2004
Date of receipt/briefing package: November 26, 2004
Date of confirmation: December 7, 2004
Date of teleconference: December 14, 2004
Type/Classification: C/Telecon/QT Interval

Meeting chair: Norman Stockbridge, M.D., Ph.D.
Meeting recorder: Denise Hinton

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products
Thomas Marciniak, M.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Division of Cardio-Renal Drug Products
Mehul Desai, M.D.	Medical Officer
Denise M. Hinton	Regulatory Health Project Manager

The Medicines Company Attendees:

Sara Nochur, Ph.D.	Sr. Director, Regulatory Affairs
Mark Sumeray, M.D.	Vice-President, Clinical Development
Bob Weiland	Surgery Team Leader
Simona Skerjanec	Director, Program Management
Bill Crouthamel, Ph.D.	Vice President, Preclinical Development
Tristan Hu	Statistician

Background:

Clevidipine was originally developed by AstraZeneca up to the completion of Phase 2 clinical studies and then was acquired by The Medicines Company. They have initiated Phase 3 testing of the product and previously met with the Division on July 28, 2004 to discuss potential NDA deficiencies that they identified in their preclinical and clinical development programs. During that meeting the Sponsor asked if the existing data were adequate to demonstrate the lack of effect of clevidipine on QT interval. The Agency stated that a thorough QT study may not be necessary if they design a phase 3 protocol that includes careful collection and analysis of QT data to show that there is enough experience in the trial to advise physicians how to manage patients with QT issues peri- or postoperatively.

The Sponsor, The Medicines Company, requested this teleconference as follow up to the preclinical meeting held on July 28, 2004 to discuss their options for the assessment of QT interval prolongation by clevidipine and a proposal to change the distribution of patients in the active comparator arms of the Phase 3 safety studies.

1. A *minimum* number of patients treated in the sodium nitroprusside (SNP) arm of 125 (originally 250),
2. A *minimum* number of patients treated in the nicardipine (NIC) arm of 125 (originally 250),
3. A *maximum* number of patients treated in the nitroglycerin (NTG) arm of 500 (originally 250).

The modifications proposed would not alter the total patient exposure to active comparator drugs (750 patients), and, importantly, do not alter the total exposure to clevidipine (750 patients).

The Division asked the Sponsor to clarify the setting in which clevidipine is to be used and also to clarify the duration of use. The Sponsor stated their existing efficacy and safety studies were conducted in the operative and perioperative setting with dosing up to 7 days.

The Division asked the Sponsor what they knew about the effects of clevidipine on blood pressure, specifically in terms of tolerance and/or rebound effects, after a "long period of sustained exposure". It was recommended that the Sponsor refer to the advisory committee minutes (June 15, 1990) on nicardipine use in the postoperative setting and consider generating a PK/PD model to assess blood pressure effects with long duration of use. The Division also suggested modeling the PK-blood pressure effect and demonstrating that there is no hysteresis of the concentration dynamic effect upon discontinuation of infusion when the treatment duration is long.

The Sponsor stated they were collecting blood pressure after discontinuation of the drug. They are looking at duration of drug administration, lab data, hemodynamic data, and adverse events. They will consider the Division's recommendation and look back over the case report forms to see if they can answer what may happen after long term exposure. They did look at short term data and no effect was seen.

The Sponsor will submit a draft of their final protocol instead of a full study protocol and plan to submit their NDA in December 2005.

Meeting recorder: {See appended electronic signature page}
Denise M. Hinton

Meeting concurrence: {See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.

Draft: 20Dec04
Final: 3Jan05

RD:

Desai: 12/23/04

Karkowsky: 12/28

Marciniak: 12/28/04

Stockbridge: 12/28

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Denise Hinton
1/4/05 08:26:30 AM

Norman Stockbridge
1/4/05 09:28:32 AM

IND 65114

Teleconference Minutes

Date: 08 September 2004

Participants

Saraswathy (Sara) V. Nochur, Ph.D.
Senior Director, Regulatory Affairs
The Medicines Company
(781) 464-1500

and

Charles A. Resnick, Ph.D.
Supervisory Pharmacologist
Division of CardioRenal Drug Products
Office of New Drugs, CDER, FDA

Subject: Clevidipine Injection; Follow-up to Division-Company Meeting of 28 July 2004

Synopsis of Conversation

Dr. Nochur called to follow up on my statement at the 28 July meeting regarding the need for segment I and III reproduction studies to support the safe use of clevidipine in _____
_____ I had said, at that time, that I would get back to her on this issue. Today, I reminded her that, based on ICH guidance, the full battery of reproductive toxicity studies is expected for all drugs that are likely to be taken by women of childbearing potential [effects on male fertility should be evaluated in any case] and that the Company should consider submitting it's best case for a waiver. The Company had, in their meeting package for the 28 July meeting, noted that a fertility (segment I) study had been done but that there were questions (raised by the Company) regarding the adequacy of that study. I asked that the study report be submitted (or resubmitted) to the Division for review. After reviewing that report and the Company's basis for a waiver, I will get back to her with a decision regarding the waiver.

C. A. Resnick, Ph.D.

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/s/

Charles Resnick
12/3/04 02:31:14 PM
PHARMACOLOGIST

Meeting between The Medicines Company and the FDA Division of Cardio-Renal Drug Products

Sponsor: The Medicines Company
IND: 65,114
Date of request: May 7, 2004
Date of receipt: May 10, 2004
Date of confirmation: May 19, 2004
Date of meeting: July 28, 2004
Time: 10:30 AM – 12:00 PM
Type/Classification: B/Toxicology/Clinical Pharmacology Issues
Meeting chair: Norman Stockbridge, M.D., Ph.D.
Meeting recorder: Denise Hinton

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products
Mehul Desai, M.D.	Medical Officer
Charles A. Resnick, Ph.D.	Team Leader, Pharmacology
Lydia Velazquez, Pharm.D.	Clinical Pharmacology/Biopharmaceutics
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry
Denise M. Hinton	Regulatory Health Project Manager

The Medicines Company Attendees:

Dr. Sol Aronson	Medical Affairs
Dr. William Clouthamel	Preclinical Development
Dr. Malcolm Lloyd	Team Leader
Dr. Clive Meanwell	Chairman
Dr. Sara Nochur	Regulatory Affairs
_____	Toxicology Consultant
Dr. James Wong	Clinical Pharmacology

Background:

The Medicines Company requested this meeting to discuss potential NDA deficiencies that they identified in their preclinical and clinical development programs and are seeking concurrence from the FDA on requirements necessary to address the deficiencies. Clevidipine was originally developed by AstraZeneca up to the completion of Phase 2 clinical studies and then was acquired by The Medicines Company. They have initiated Phase 3 testing of the product and plan to file their NDA in 2005.

Discussions:

The Division provided responses to the Sponsor's questions as follows:

- 1. Does the Agency concur that the lack of evaluation of the E.coli strain in the Ames Salmonella/mammalian microsome test does not impact on the adequacy of the test?**

No, the Agency does not concur. The strains should be tested with and without formaldehyde dehydrogenase. Formaldehyde is a product of clevidipine metabolism. A positive Ames Test in

The Division concurs that further drug interaction studies specific to cytochrome P450 are not required.

7. Does the Agency concur with the rationale that clevidipine administered at clinically relevant doses will have no detectable effect on the endogenous levels of formaldehyde?

The Agency does not concur and asked where the formation of formaldehyde and subsequent distribution of it takes place. The Sponsor explained that the drug is metabolized by esterases and available data shows that the drug is metabolized in fresh human blood. The proposed pharmacokinetic formaldehyde study will not provide information as to where the conversion of clevidipine to formaldehyde takes place and whether the formation of formaldehyde is distributed and centralized in a specific organ. As a result, the Agency recommended that an animal study with radiolabeled clevidipine would best answer this question..

8. If no to Question 7, does the Agency concur with the proposed study design in healthy volunteers for determination of formaldehyde and formic acid after clevidipine administration?

As discussed above, the proposed pharmacokinetic formaldehyde study will not provide information as to where the conversion of clevidipine to formaldehyde takes place and whether the formation of formaldehyde is distributed and centralized in a specific organ. As a result, the Agency has recommended that an animal study with radiolabeled clevidipine be conducted.

9. Does the Agency concur that the existing data are adequate to demonstrate the lack of effect of clevidipine on QT interval?

The Agency stated that a thorough QT study may not be necessary for this product if the Sponsor designs a phase 3 protocol that comprises careful collection and analysis of QT data. The information should show that there is enough experience in the trial to advise physicians, in labeling, how to manage patients with QT issues peri- or postoperatively.

The Sponsor expressed concern over the Agency's proposal and stated that confounding factors (e.g. perioperative setting, electrolyte shifts, concomitant drugs) will have an effect on the QT interval and will introduce noise into the results. They agreed to talk with those who are running the trial to see if it may be more advantageous to conduct a thorough QT study.

Meeting recorder: *{See appended electronic signature page}*
Denise M. Hinton

Meeting concurrence: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Draft: 29Jul04
Final: 10Aug04

RD: 3Aug04
Velazquez 8/4/04
Resnick 8/9/04
Desai 8/9/04
Karkowsky8/9/04
Stockbridge 8/10/04

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/s/

Denise Hinton
8/10/04 08:44:40 AM

Norman Stockbridge
8/10/04 05:13:16 PM

Meeting between The Medicine's Company and the FDA Division of Cardio-Renal Drug Products

Sponsor: The Medicine's Company
Drug: Clevidipine Injection (0.5 mg/mL)
IND: 65,114
Date of request: June 18, 2003
Date of confirmation: July 1, 2003
Date briefing document received: June 17, 2003
Date of meeting: August 28, 2003
Type: B
Classification: Pre-phase 3

FDA Participants:

Douglas C. Throckmorton, M.D. Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D. Deputy Director, Division of Cardio-Renal Drug Products
Mehul Desai, M.D. Medical Officer
Charles Resnick, Ph.D. Pharmacology Team Leader
Pritam Gill-Kumar, M.D. Pharmacologist
Patrick Marroum, Ph.D. Biopharmaceutists Team Leader
Denise M. Hinton Regulatory Health Project Manager

The Medicines Company Participants:

Malcolm Lloyd, M.D. Project Leader
Clive Meanwell, M.D. Ph.D. Executive Chairman, TMC
Sara Nochur, Ph.D. Senior Director, Regulatory Affairs
John Richards, Ph.D. V-P, Manufacturing Operations
Andrew Sternlicht, M.D. Executive Medical Director
John Villiger, Ph.D. Vice President, Product Development
James Wong, Ph.D. Director, Clinical Pharmacology.

Background:

As a follow-up to the pre-Phase 3 meeting held on March 25, 2003, The Medicines Company (TMC) requested this teleconference to discuss the following issues pertaining to the preclinical testing for clevidipine:

1. Retest of the mouse micronucleus assay
2. Testing for formaldehyde concentration in clinical studies
3. Conduct of cytochrome P450 induction and inhibition studies
4. Drug interaction studies with clevidipine
5. Conduct of a pharmacokinetic study in patients with renal impairment

Discussions:

Mouse Micronucleus Study

The Division finds the test done at the 48-hour harvest time for the mouse micronucleus test acceptable.

Cytochrome P450 Studies

In regard to cytochrome P450 induction and inhibition studies, the submitted draft protocols are acceptable and appropriate.

Drug Interaction Studies

The Sponsor requested clarification on whether the proposal to study potential drug interactions as part of the Phase 3 safety program would meet FDA requirements. The Division recommended that the Sponsor meet with the Division for discussion when the results of the study are available for review.

Formaldehyde Measurement in Blood

The Division commented on the Sponsor's proposal to not measure formaldehyde levels in the blood. The Sponsor claimed that it would be difficult to measure formaldehyde concentrations, but cited a label of the product, Cerebyx (fosphenytoin), which included detailed information on the concentration, suggesting that it is possible under some circumstances. The Division stated that it would be reasonable to have a measure of formaldehyde/formate during the course of development. It will be necessary to have direct measurements in at least some patients to alleviate concerns of formaldehyde/formate accumulation.

The Sponsor stated that the study would measure formic acid, not formaldehyde, as formaldehyde assays had not been validated and literature shows conversion of formaldehyde to formic acid to be very rapid. The Division stated that it would be the Sponsor's case to make that the measurement of formic acid is superior to the measurement of plasma levels of formaldehyde. If the Sponsor is successful in making their case and resolves the concern over the formation of formaldehyde/formate, then the proposal would be acceptable.

The Sponsor stated that they would consider the Division's recommendation of adding formaldehyde dehydrogenase to all plasma samples to ensure that formaldehyde is converted to formic acid. The Sponsor will submit their protocol to directly measure formaldehyde exposure and schedule future discussions after the Division has had an opportunity to review the information. The Sponsor should make a fuller case for the numbers in the tables provided in the briefing document, supporting the levels anticipated from the product, and make an effort to directly measure formaldehyde concentrations.

The Sponsor affirmed that formaldehyde is not a degradant of clevidipine and is formed only when clevidipine is metabolized in-vivo.

Drug Interaction Studies

The need for drug-drug interaction studies should be discussed with the Division after the results of in vitro testing discussed above are available.

PK Study

The Division agrees with the Sponsor's argument that it is not necessary to conduct a PK study in patients with impaired renal function due to the short duration and rate of exposure with clevidipine.

In response to the Sponsor's question of whether they could use healthy volunteers in the study, the Division stated that it would be acceptable.

Meeting recorder: _____
Denise M. Hinton

Meeting concurrence: _____
Douglas C. Throckmorton, M.D.

Draft: 29Aug03

Final: 5Sep03

RD: 2Sep03

Gill Kumar 2Sep03

Resnick car 9/2/03

Marroum 9/2/03

Desai 4Sep03

Stockbridge 9/5/03

Throckmorton 9/5/03

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/s/

Denise Hinton

9/5/03 11:29:25 AM

Minutes signed off by Dr. Throckmorton and faxed to
the Sponsor on 5Sep03.

Meeting between The Medicine's Company and the Division of Cardio-Renal Drug Products

Sponsor: The Medicine's Company
IND: 65,114
Date of request: December 12, 2002
Date of confirmation: January 6, 2003
Date briefing package received: February 24, 2003
Date of meeting: March 25, 2003
Time: 1:30 PM – 3:00 PM
Classification: B

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products
Mehul Desai, M.D.	Medical Officer
Pritam Gill-Kumar, M.D.	Pharmacologist
Lydia Velazquez, Pharm.D.	Clinical Pharmacology and Biopharmaceutics
Denise M. Hinton	Regulatory Health Project Manager

The Medicines Company Attendees:

Clive Meanwell, M.D., Ph.D.	Executive Chairman
Sara Nochur, Ph.D.	Sr. Director, Regulatory Affairs
Andrew Sternlicht, M.D.	Medical Director
John Villiger, Ph.D.	VP, Managing Director
Lisa-Sue Wood	Manager, Regulatory Affairs
Malcolm Lloyd, M.D.	Director, Business Development & Medical Affairs

Background:

The Medicines Company (TMC) requested this meeting to discuss the clinical development plan for clevidipine, a short-acting L-selective calcium channel antagonist, with the ability to acutely lower blood pressure. The focus will be on finalization of the indication and the study design for the proposed pivotal Phase 3 clinical trials.

Discussion:

1. Is the proposed indication acceptable to the FDA?

Four handwritten checkmarks are present below the question, indicating that the proposed indication is acceptable to the FDA.

2. If the data from the efficacy and safety studies as proposed are positive and the endpoints of the trial as agreed upon are achieved, would the studies be considered suitable in support of an NDA approval of the proposed indication?

/ / / / /

3. Feedback on the design of the studies:

i. *Study Design and Endpoints of the Efficacy Studies:* The Agency's opinion regarding the breakdown of the efficacy studies into two trials, one studying the treatment of hypertension preoperatively, and the second studying the postoperative treatment of hypertension. We would appreciate comments, if any, on the primary endpoint in both studies, which will be a comparison of the therapeutic response (no bailout) in the clevidipine versus placebo arms.

▪ **FDA response: The study design and endpoints of the efficacy studies are acceptable. The use of a need for "bailout" treatment as the primary endpoint seems appropriate here, especially provided the efficacy trials can be sufficiently well blinded (see below).**

ii. *Safety Endpoint/Sample Size:* Agency acceptance of the design of the proposed safety studies with active comparator, including sample size.

Comparators: Nitroglycerin and sodium nitroprusside are commonly used in the U.S. for the perioperative control of hypertension during cardiovascular surgery (Vuylsteke et al, 2000). Intravenous nicardipine is a dihydropyridine calcium channel blocker that has been used in the control of postoperative hypertension (IV Nicardipine Study Group) and is indicated in the short-term treatment of hypertension when oral therapy is not feasible or not desirable. It is our opinion that use of these three agents as active comparators in the proposed safety studies realistically represents current medical practice.

▪ **FDA response: The TMC was advised and agreed to have a central committee to adjudicate myocardial infarctions. The three most widely-used agents seem appropriate posture controls, although there was discussion of the use of an agent in a**

separate class (enalaprilat). The sponsor thought its use was limited by its pharmacodynamic half-life but would look into it further.

- iii. *Blinding*: We propose blinding the two efficacy studies using clevidipine lipid emulsion vehicle (Intralipid®). For the three safety studies, we propose conducting open-label studies with monitoring of all adverse events including serious AEs such as death, MI, stroke and renal dysfunction at 30 days. We are proposing open-label safety studies for the following reasons:

Clevidipine is insoluble in water and is formulated in a 20% lipid emulsion, which imparts a white, opaque color to it. All active comparators are in clear aqueous solution, which makes double blinding in the operating room and intensive care unit difficult. However, two possible "blinding" solutions could be employed:

- a) A double dummy method (as used in previous AstraZeneca studies and the ongoing TMC study TMC-CLV-02-01). However, as stated in the Agency's letter dated 08/02/02 to The Medicines Company, there is a concern that if we were to conduct a double-blind study with a comparator, the employment of a double dummy blinding technique involving the administration of Intralipid along with the comparator drug is likely to mask any adverse effects due to Intralipid in the clevidipine arm.
- b) Another blinding method is to mask the bag/syringe/tubing, for example, by covering the bag and tubing with foil. However, this poses other issues such as maintaining the mask, which may be broken due to spillage of fluid, the foil coming off, breaks in the foil, etc., as well as the lack of visual control of the infusion to confirm that drug administration is taking place and without problems (e.g. there are no air bubbles in the line).

FDA response: The double-blind procedures for the efficacy trials and the planned open label safety experience studies are acceptable. For the safety studies there should be blinded central adjudication of the SAES.

Additional points of discussion:

- **The Division advised TMC to address cardiac effects on the QT interval by use of Holter monitoring.**

The Division advised TMC to determine whether intralipid had an acute effect on blood pressure, as the drug will only be administered with that vehicle and it would be important to characterize the effects of both parts of the 'combination' in the event the sponsor wants to use a different vehicle in the future.

From the Clinical Pharmacology and Biopharmaceutical viewpoint, the following issues were addressed at the meeting:

- **The sponsor will have to address enantiomer activity and how it relates to efficacy and safety.**
 - **In vitro metabolic studies should be carried out to determine if clevidipine induces/inhibits any of the P450 enzymes.**
 - **The sponsor was encouraged to contact the Clinical Pharmacology and Biopharmaceutics team for guidance on the drug interaction studies that should be conducted based on the in-vitro results obtained.**
 - **If, as a result of these findings, special population studies are required, we encouraged the sponsor to contact us as well.**
-
- **The Division stated that pending full review of TMC's data, the submitted information regarding protein-binding, the reduction of body temperature, and identified inactivity towards efficacy pharmacodynamically was acceptable. TMC should pursue further discussion with the Biopharmaceutists at a later date to discuss requirements.**
 - **The Division stated that it would be important to assess whether formaldehyde accumulated during treatment with clevidipine. Therefore, TMC should determine the plasma levels of formaldehyde in patients before the start of treatment, at the end of treatment, and at one or two suitable time points after the end of treatment.**

**Meeting recorder: _____
Denise M. Hinton**

**Meeting concurrence: _____
Robert Temple, M.D.**

**Draft: 1Apr03
Final: 22Apr03**

RD:

Temple 4/21/03

Throckmorton 4/11/03

Stockbridge 4/8/03

Desai 4/7/03

Velazquez 4/7/03

Gill-Kumar 4/4/03

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/s/

Denise Hinton

4/23/03 10:09:57 AM

Minutes signed by Dr. Temple on 22Apr03 and faxed
to the sponsor on 23Apr03.



IND 65,114

The Medicines Company
Attention: Sonja Barton Loar, Ph.D.
One Cambridge Center
Cambridge, Ma 02142

Dear Dr. Loar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Clevidipine Injection 0.5 mg/ml.

We also refer to your amendment dated September 18, 2002 (serial # 001), submitted in response to our letter dated August 20, 2002 containing pharmacology and toxicology studies that were referenced in the Investigators' Brochure and studies reviewed under IND 50,261 for clevidipine.

We have completed the review of your submission and have the following comments and requests for additional information. Please note that these requests are not clinical hold issues. However a response is requested.

1. We note that the Mouse micronucleus test did not follow the animals for the standard exposure duration (72 hours). We recommend that you repeat the Mouse micronucleus test using 24, 48, and 72 hour harvest times for the vehicle and the clevidipine groups. If a clevidipine dose of 200 μ M/kg does not produce mortality, then 200, 100, and 20 μ M/kg doses of clevidipine should be used. Otherwise, the test should be repeated using the doses used in study #95115.
2. You propose that formaldehyde, formed as a part of clevidipine metabolism, is responsible for the observed genotoxic effect of the drug. Please comment on the possibility of any role for the measurement of formaldehyde levels in the clinical trials and any such testing you plan to conduct.

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5333

**APPEARS THIS WAY
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Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton
3/6/03 02:01:58 PM



IND 65,114

The Medicines Company
Attention: Ms. Sonja Barton Loar, Ph.D.
One Cambridge Center
Cambridge Center, Massachusetts 02142

Dear Ms. Loar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Clevidipine Injection (H324/38).

We have completed the clinical, chemistry, and pharmacology reviews of your submission and have the following comments and requests for additional information. Please note that these requests are not clinical hold issues. However, response to them is requested.

1. Per protocol TMC-CLV-02-01, a 70 kg patient receiving the maximum possible dose of clevidipine at $8\mu\text{g}/\text{kg}/\text{min}$ for 2 hours and $4.3\mu\text{g}/\text{kg}/\text{min}$ for 16 hours would receive approximately 713 ml of 20% lipid emulsion in 18 hours. According to the package insert for Intralipid, a 20% lipid emulsion used to provide parental nutrition for extended periods of time, not more than 500 ml should be infused on the first day.
2. On page 31 of the protocol it states for the Intralipid not to be infused at a rate exceeding 1.6 mL/min. In addition to a maximal infusion rate, the Division recommends you cite the restriction in terms of no more than 500 mL Intralipid be exceeded in 24 hours. You should also consider a 1 mg/mL formulation. With this formulation, a patient requiring the maximum dose would only receive 350 ml of the lipid emulsion.
3. Page 29 of the protocol states that patients randomized to nitroglycerin will also receive Intralipid in order to preserve blinding. This may mask any adverse effects due to lipid in the clevidipine group. Patients who are not randomized to clevidipine would unnecessarily receive Intralipid and might incur some risk due to IV Intralipid administration. The Division recommends you consider a method to protect blinding without administering Intralipid to patients randomized to nitroglycerin.
4. Please submit full reports of the following studies:
 - 1) General pharmacology studies referenced on pages 18-27 of the Investigator Brochure.

2) The mutagenicity studies referenced on pages 36-37 of the Investigator Brochure.

- a) Chromosome aberration assay in human lymphocytes
- b) Lymphocyte transformation test
- c) Mouse micronucleus test

If you have any questions, please call:

Denise Hinton
Regulatory Project Manager
(301) 594-5312

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton
8/20/02 05:42:00 PM

Minutes of a 30-Day Safety Meeting

IND: 65,114
Drug: Clevidipine Injection 0.5 mg/mL
Date of Meeting: July 16, 2002
Sponsor: The Medicine's Company
Date of Application: June 26, 2002
Meeting Chair: Norman Stockbridge, M.D., Ph.D.

Meeting Participants:

Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical Officer, HFD-110
Mehul Desai, M.D.	Medical Officer, HFD-110
Pritam Gill-Kumar, Ph.D.	Pharmacologist, HFD-110
Monica Cooper, Ph.D.	Chemist, HFD-810/110

Background

The Medicines Company entered into agreement with AstraZeneca PLC for the licensing, development and commercialization of clevidipine. The AstraZeneca development program was conducted under IND #50,261. AstraZeneca submitted a letter allowing the FDA to reference IND 50,261 on behalf of the Medicines Company as well as a cross-reference letter from the manufacturer, _____ to reference DMF# _____

Clevidipine Injection, a racemic mixture synthesized at the research laboratories at Astra Hassle, is being studied for _____ Clevidipine is an ultra short-acting, vascular selective calcium antagonist, intended for _____

The sponsor proposes to conduct a double blind prospective randomized comparison of clevidipine versus nitroglycerin for blood pressure control and preservation of renal function in patients undergoing Coronary Artery Bypass Graft (CABG) Surgery.

Meeting

Chemistry

There are no chemistry safety issues.

Pharmacology/Toxicology

Dr. Pritam Gill-Kumar had the following concerns:

- As per protocol TMC-CLV-02-01, a 70-kg patient receiving the maximum doses (8 µg/kg/min for 2 hours, and 4.3 µg/kg/min for 16 hours), would receive 713 ml 20% lipid in 18 hours. The maximum 24-hour infusion of an intralipid (according to the package insert) should not exceed 500 ml on the first day.
- In the protocol, the sponsor states that the intralipid recommendation is that the rate should not exceed 1.6 ml/min, however there is not any mention of no more than 500 ml of the intralipid should be given within 24 hours. The sponsor should cite the restriction in the protocol.

- The sponsor should consider a 1 mg/ml formulation. With this formulation, a patient requiring the maximum dose would only receive 350 ml lipid.
- According to the protocol, patients randomized to nitroglycerin will also receive intralipid in order to preserve blinding and may possibly mask any adverse side effects due to lipid in the clevidipine group. Patients who are not randomized to clevidipine would unnecessarily receive intralipid and might incur some risk due to IV intralipid administration. The sponsor should devise a method to protect the blind without having to administer intralipid to patients randomized to nitroglycerin.

Dr. Pritam requests for the sponsor to submit full reports of the following studies which are referenced in the Investigator Brochure, submitted with this IND:

General pharmacology studies referenced on pages 18-27 of the Investigator Brochure.

Mutagenicity studies referenced on pages 36-37 of the Investigator Brochure.

- a) Chromosome aberration assay in human lymphocytes
- b) Lymphocyte transformation test
- c) Mouse micronucleus test

The above recommendations will be conveyed to the sponsor. There are no clinical hold issues.

Clinical

The package insert for Intralipid® states that no more than 500 ml should be administered on the first day of therapy. Dr. Desai stated that his only safety concern is that the sponsor did not state the maximum amount of Intralipid that can be administered in one day to a patient. Dr. Stockbridge concurs.

The safety concern will be conveyed to the sponsor in writing. There are no clinical hold issues.

Biopharmaceutics

There are no biopharmaceutical issues to be addressed.

Recommendations

The pharmacology and clinical concerns discussed above will be conveyed to the sponsor.

Conclusion

The Medicines Company may proceed with the proposed study.

Meeting Recorder:

Denise M. Hinton

Concurrence Chair:

Norman Stockbridge, M.D., Ph.D.

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/s/

Norman Stockbridge
8/19/02 10:47:34 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,114

The Medicines Company
Attention: Sonja Barton Loar, Pharm.D.
One Cambridge Center
Cambridge, MA 02142

Dear Dr. Loar:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 65,114

Sponsor: The Medicines Company
Name of Drug: Clevidipine Injection (H324/38)
Date of Submission: June 26, 2002
Date of Receipt: June 27, 2002

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before July 27, 2002, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

IND 65,114

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Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call me at (301) 594-5312.

Sincerely yours,

Denise Hinton
Regulatory Project Manager
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Denise Hinton

7/12/02 10:45:35 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,114

The Medicines Company
Attention: Sonja B. Loar, Pharm.D.
One Cambridge Center
Cambridge, MA 02142

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Sincerely,

{See appended electronic signature page}

Ms. Denise M. Hinton
Regulatory Health Project Manager
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research