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**APPLICATION NUMBER: 020287/S010**

**ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS**

Oliver

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

MAY 25 1999

**Application Number:** NDA 20-287/S-010

**Name of Drug:** Fragmin® (dalteparin sodium injection)

**Sponsor:** Pharmacia & Upjohn

**Material Reviewed**

**Submission Date(s):** April 12, 1999

**Receipt Date(s):** April 13, 1999

**Background and Summary Description:**

Supplement 010, submitted May 29, 1998, provides for a proposed new indication, "the treatment of unstable angina and non-Q-wave myocardial infarction for the prevention of ischemic complications in patients on concomitant aspirin therapy."

**Review**

**Package Insert**

The draft labeling, with no identification code, was compared to the labeling approved March 30, 1999 in Supplement 008. The package insert was identical except for the following:

1. In the CLINICAL PHARMACOLOGY section:
  - a. In the "Pharmacodynamics" subsection, in the second sentence of the first paragraph, the abbreviation "s.c." was added after the word "subcutaneous" to read: "subcutaneous (s.c.)". Thereafter, in the text throughout the package insert, the abbreviation "s.c." was used.

**These changes are ACCEPTABLE.**

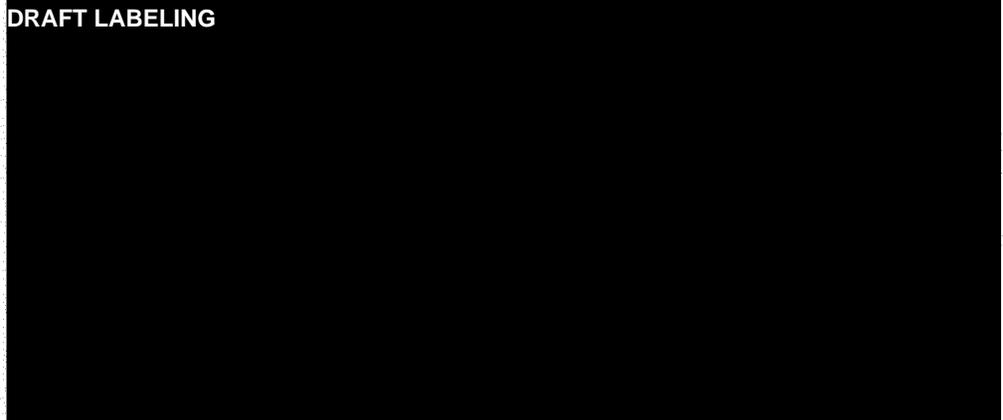
- b. In the "Pharmacokinetics" subsection, in the third sentence of the fourth paragraph, the abbreviation "hr" was changed to "hour". Thereafter, in the text throughout the package insert, the abbreviation "hr" was used.

**These changes are ACCEPTABLE.**

2. In the CLINICAL TRIALS section:

- a. A new, and the first subsection of the section, entitled "Unstable Angina and Non-Q-wave Myocardial Infarction"; text describing the two pivotal trials supporting the indication; and "Table 1", entitled "Efficacy of FRAGMIN in Unstable Angina and Non-Q-wave Myocardial Infarction", were provided in the subsection as follows:

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DRAFT LABELING

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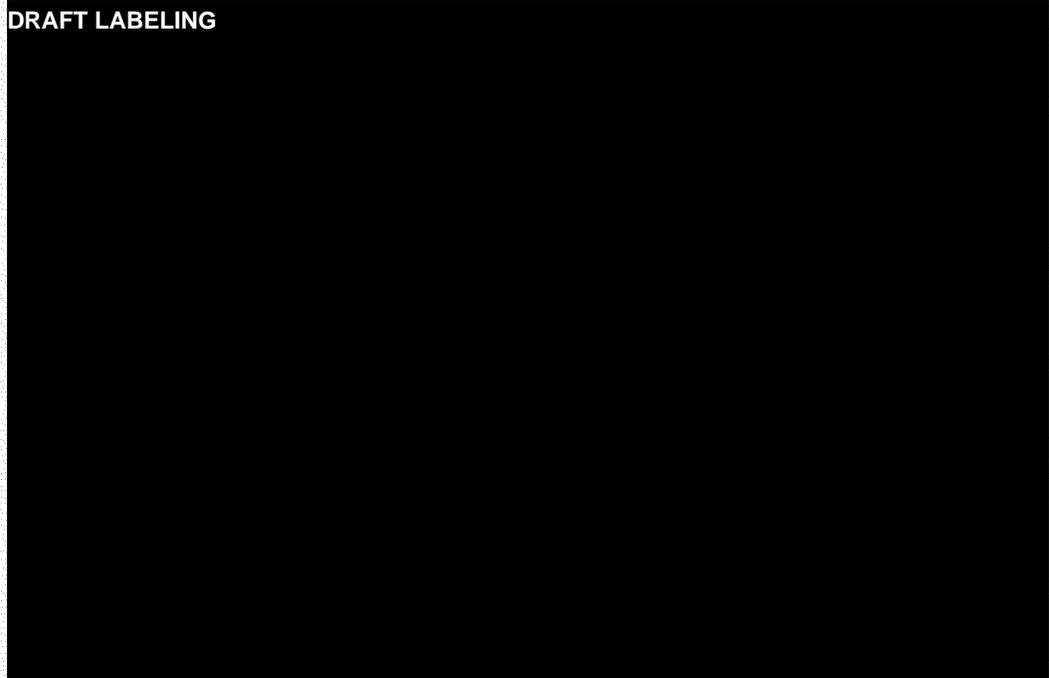
NDA 20-287/S-010

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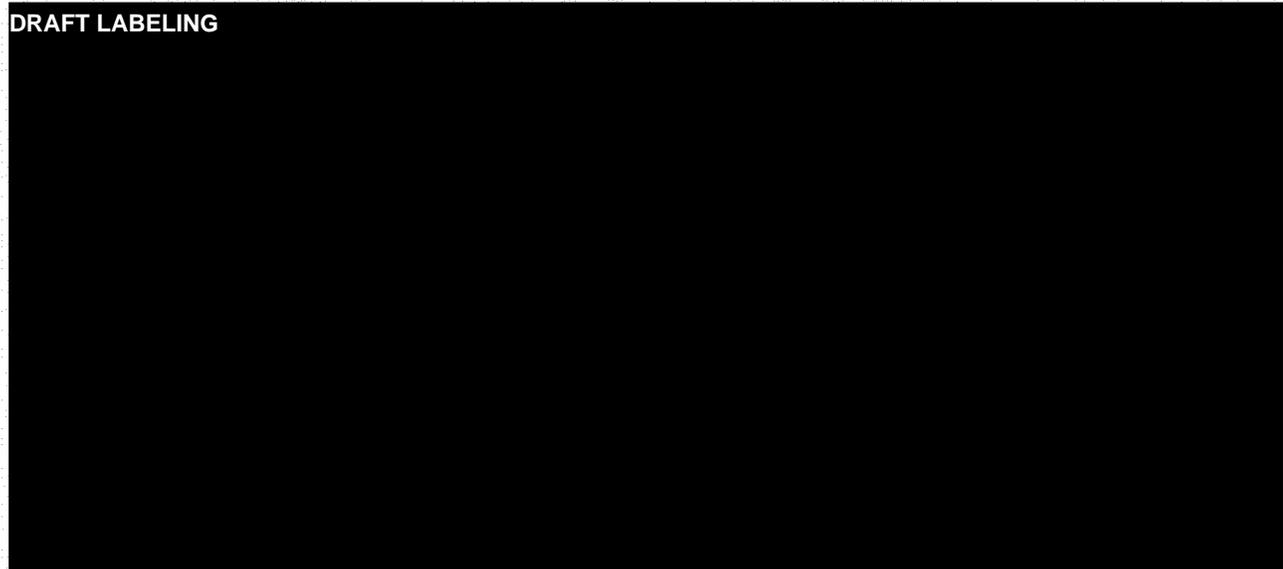
A large black rectangular redaction box covering the majority of the page content below the first 'DRAFT LABELING' header.

**This additional information was reviewed by the MEDICAL OFFICER, Dr. John Schmeling, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and should be revised as follows:**

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- b. The "Abdominal Surgery" subsection, previously the first subsection in the CLINICAL TRIALS section, was moved to be the third subsection, and the "Hip Replacement Surgery" subsection was maintained as the second subsection. Consequently, the tables were re-numbered sequentially, and references to the tables within the text were appropriately changed. Throughout the other sections of the text, the order of reference to specific indications is maintained as follows: "unstable angina", "abdominal surgery, and "hip replacement".

**These changes are ACCEPTABLE.**

- c. In the "Abdominal Surgery" subsection, in the first sentence of the subsection, the underlined words were changed:

from:

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to:

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**These changes are ACCEPTABLE.**

- d. In the "Efficacy of FRAGMIN in Abdominal Surgery" Tables, the words "versus placebo" and "versus heparin" were deleted from the subscript 1 in the two data tables to read: "p-value=0.008" and "p-value = 0.74" respectively.

**These deletions are ACCEPTABLE.**

- e. In the "Hip Replacement Surgery" subsection, in the second paragraph, the third sentence, the underlined text was changed

from:

DRAFT LABELING

to:

DRAFT LABELING

**This change was reviewed by the MEDICAL OFFICER, Dr. John Schmeling, and the DIVISION DIRECTOR, Dr. Lilia Talarico. The sponsor should be requested to verify the p value (p= 0.010 or p= 0.01.)**

3. In the INDICATIONS AND USAGE section:

- a. The following indication was added as the first paragraph if the section to read:

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**This additional information was reviewed by the MEDICAL OFFICER, Dr. John Schmeling, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and should be revised as follows:**

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- b. In the second paragraph, the first sentence, the word "Injection" was deleted after the word "FRAGMIN" and word "also" was added to read:

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**These changes are ACCEPTABLE.**

4. In the CONTRAINDICATIONS section, the following paragraph was added as the second paragraph of the section to read:

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**This additional information was reviewed by the MEDICAL OFFICER, Dr. John Schmeling, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and should be revised as follows:**

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5. In the WARNINGS section, in the "Thrombocytopenia" subsection, the first sentence was changed

from:

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to:

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**These changes were reviewed by the MEDICAL OFFICER, Dr. John Schmeling, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and should be revised as follows:**

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6. In the PRECAUTIONS section:

a. In the "Drug Interactions" subsection, the underlined sections of the sentence were changed

from:

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to:

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**These changes were reviewed by the MEDICAL OFFICER, Dr. John Schmeling, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and should be revised as follows:**

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- b. In the "Nonteratogenic Effects" subsection, in the second sentence, the word "multi-dose" was changed to "multiple-dose" in the following sentence to read:

The 9.5 mL multiple-dose vial of FRAGMIN contains 14 mg/mL of benzyl alcohol.

**This change is ACCEPTABLE.**

7. In the ADVERSE EVENTS section:

- a. In the "Hemorrhage" subsection:

1. In the second paragraph, the word "study" was changed to the word "trial" to read: "In a trial comparing..."

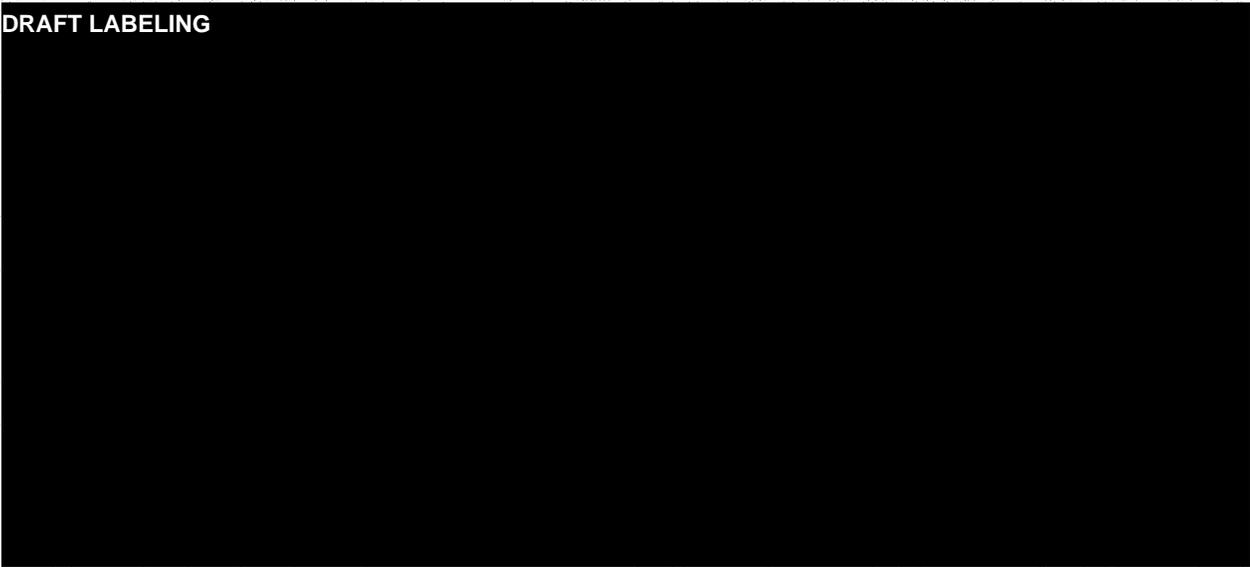
**This change is ACCEPTABLE.**

- b. The following sub-subsection heading and text were added to read:

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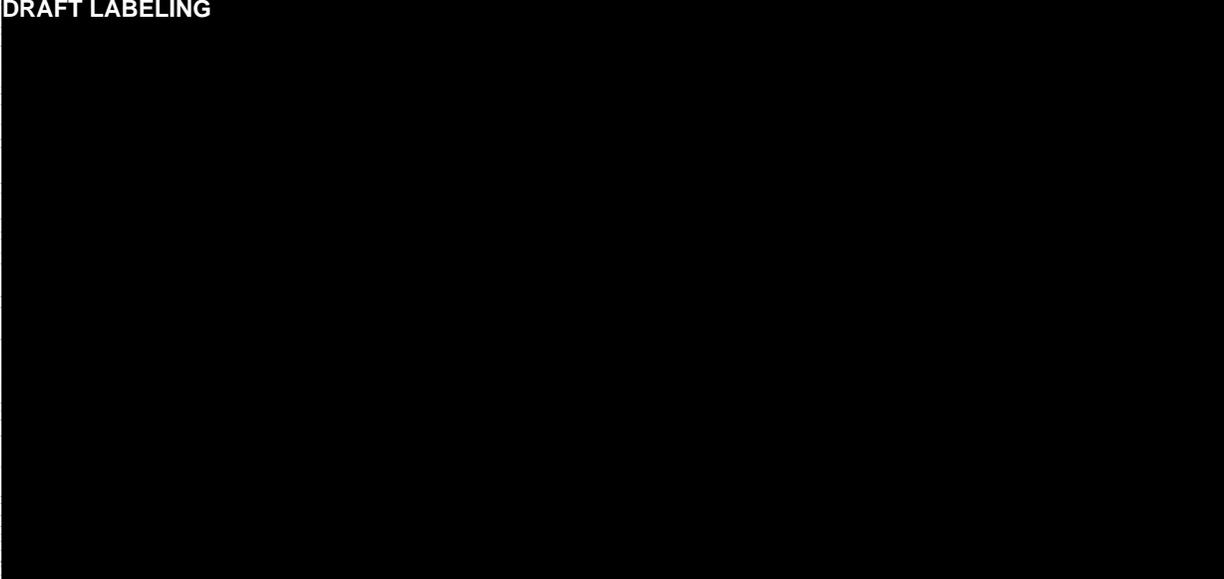


**This additional information was reviewed by the MEDICAL OFFICER, Dr. John Schmeling, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and should be revised as follows:**

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- c. In the "Other" subsection, the "Ongoing Safety Surveillance" sub-subsection, the number "5" in the text was changed to the word "five".

**This change is ACCEPTABLE.**

- 8. In the DOSAGE AND ADMINISTRATION section:

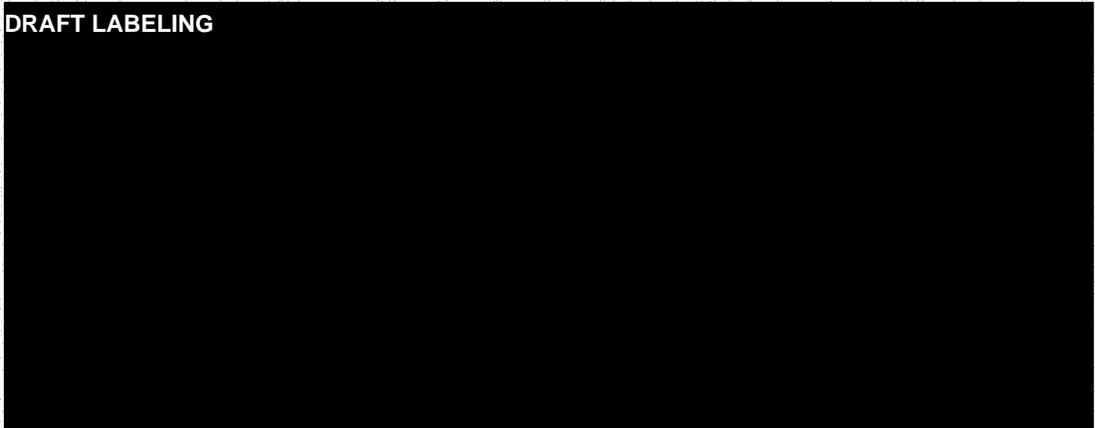
- a. A new subsection, "Unstable Angina and Non-Q-wave Myocardial Infarction" and text was inserted to read:

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**This additional information was reviewed by the MEDICAL OFFICER, Dr. John Schmeling, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and should be revised as follows:**

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- b. In the "Hip Replacement Surgery" subsection, the second paragraph was moved from the subsection, and placed as the second paragraph of the "Abdominal Surgery" subsection.

**This change should is ACCEPTABLE.**

- c. In the "Abdominal Surgery" subsection, the underlined words in the first paragraph were changed

from:

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to:

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**This change is ACCEPTABLE.**

9. In the HOW SUPPLIED section, the subsection title "Storage" was deleted.

**This change is ACCEPTABLE.**

**Conclusions**

1. The following changes are ACCEPTABLE: 1.a., 1.b., 2.b., 2.c., 2.d., 3.b., 6.b., and 7.a., 7.c., 8.b., 8.c., and 9.
2. The following changes were reviewed by the MEDICAL OFFICER and the Division Director, and require revisions: 2.a., 2.c., 2.e., 3.a., 4., 5., 6.a., 7.b., and 8.a.
3. The text of the package insert labeling was negotiated with the sponsor on May 24 and May 25, 1999 via facsimile. For specific revisions, i.e. strikeout for deletion of text and underlining for the addition of text, see Attachment 1.

/s/ [REDACTED] 05/25/99

Karen Oliver  
Regulatory Health Project Manager

Concurrence:

/s/ [REDACTED]

Lilia Talarico, M.D. 5-25-99  
Division Director

Attachments: (1)

[REDACTED] APPEARS THIS WAY ON ORIGINAL

cc:

Original NDA 20-287/S-010  
HFD-180/Div. Files  
HFD-180/K.Oliver  
HFD-180/L.Talarico  
HFD-180/J.Schmeling

draft: KO/April 16, 1999

r/d Initials: L.Talarico 05/25/99

final: KO/05/25/99/c:\mydocuments\NDA20287-S-010-04-16-99-labrev

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NDA 20-287/S-010

Pharmacia & Upjohn  
Attention: Mr. James H. Chambers  
7000 Portage Road  
Kalamazoo, Michigan 49001

JUN 15 1998

Dear Mr. Chambers:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Fragmin® (dalteparin sodium injection)

NDA Number: 20-287

Supplement Number: S-010

Therapeutic Classification: Standard (S)

Date of Supplement: May 29, 1998

Date of Receipt: June 1, 1998

This supplement proposes the following change(s): the addition of a new indication, "the treatment of unstable angina and non-Q-wave myocardial infarction for the prevention of ischemic complications in patients on concomitant aspirin therapy."

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 31, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 1, 1999.

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: DOCUMENT CONTROL ROOM, 6B-24  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, contact me at (301) 443-0487.

Sincerely,

/s/ [REDACTED]

Karen Oliver, RN, MSN  
Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 20-287/S-010

HFD-180/Div. Files

HFD-180/K.Oliver

DISTRICT OFFICE

Drafted by: KO/June 15, 1998

final: KO/June 15, 1998

filename: c:\wpfiles\mydocuments\NDA20287-6-15-98-S-010-acksupp

/s/ [REDACTED]

06/15/98

SUPPLEMENT ACKNOWLEDGEMENT (AC)

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Exclusivity Summary Form

(Modified: October 14, 1998)

EXCLUSIVITY SUMMARY FOR NDA # 20-287 SUPPL # 010

Trade Name: Fragmin Generic Name: dalteparin sodium injection

Applicant Name: Pharmacia & Upjohn Company HFD # 180

Approval Date If Known: May 25, 1999

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /  / NO /  /

b) Is it an effectiveness supplement?

YES /  / NO /  /

If yes, what type? (SE1, SE2, etc.) SE 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:

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

Form OGD-011347 Revised 8/27/97  
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /  / NO /  /

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

\_\_\_\_\_

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

YES /  / NO /  /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /  / NO /  /

IF THE ANSWER TO QUESTION 3 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# 20-287 Fragmin (dalteparin sodium injection)

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. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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 /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

FRESC TRN 91-115

ERIC TRN 91-128

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #  YES /  / NO /  / Explain: \_\_\_\_\_

Investigation #2

IND #  YES /  / NO /  / Explain: \_\_\_\_\_

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /  / Explain \_\_\_\_\_ NO /  / Explain \_\_\_\_\_

Investigation #2

YES /  / Explain \_\_\_\_\_ NO /  / 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: \_\_\_\_\_

Signature: [Redacted]

Date: 05/25/99

Title: Regulatory Health Project Manager

Signature of Office/Division Director

Signature: [Redacted]

Date: 5-25-99

cc: Original NDA Division File HFD-93 Mary Ann Holovac

NDA 20-28715-010

Previous Page

HFD-180 Div File

HFD-180 K. Oliver

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