CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020297 (S-005)

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling				X
Medical Review(s)				X
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020287 (S-005)

APPROVAL LETTER

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287 (S-005)

ADMINISTRATIVE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-287/S-005

SEP 24 1996

Name of Drug: Fragmin® (dalteparin sodium injection)

Sponsor: Pharmacia & Upjohn

Material Reviewed

Submission Date(s): May 16, 1996

Receipt Date(s): May 17, 1996

Background and Summary Description: The supplement provides for labeling changes in the DOSAGE AND ADMINISTRATION and the HOW SUPPLIED sections of the package insert regarding an autoinjector device, Fragminject™, available for use with Fragmin syringes.

Review

The submitted draft labeling, identified as "132010496 Revised April 25, 1996", was compared to the final printed labeling, identified as "132010396 Revised March 20, 1996", approved March 18, 1996 in supplement 003. The inserts were identical except for the following:

1. The identification codes were changed.

   This editorial change is ACCEPTABLE.

2. In the DESCRIPTION section, the format of the structural formula was changed.

   This change, reviewed by the CHEMIST, Dr. Joseph Sieczkowski, is ACCEPTABLE.

3. In the DOSAGE AND ADMINISTRATION section, the "Administration" subsection:

   a. In the following sentence, the bolding was deleted from the word "must" to read: "When the area around the navel or the thigh is used, using the thumb and forefinger, you must lift up a fold of skin while giving the injection."

      This editorial change is ACCEPTABLE.

b. The following sentence was added: "An autoinjector, Fragminject, is available for patients to administer daily Fragmin injections in an out-patient setting."

The addition, reviewed by the MEDICAL OFFICER, Dr. Lilia Talarico, is UNACCEPTABLE. The sentence should be revised to read: "An autoinjector, Fragminject, is available for patients to administer daily Fragmin injections."

4. In the HOW SUPPLIED section, the following sentence was added: "Please see directions accompanying the Fragminject autoinjector."

This addition, reviewed by the MEDICAL OFFICER, Dr. Lilia Talarico, is UNACCEPTABLE in the HOW SUPPLIED section. The sentence should be moved to the DOSAGE AND ADMINISTRATION section, the "Administration" subsection, to read as follows: "An autoinjector, Fragminject, is available for patients to administer daily Fragmin injections." "Please see directions accompanying the Fragminject autoinjector."

5. After the HOW SUPPLIED section:

a. The words "manufactured", "distributed by", "Pharmacia", and "Pharmacia Inc." were changed from capital and small letters to all capital letters.

This editorial change is ACCEPTABLE.

b. The bolding was deleted from the words "Pharmacia AB" and "Pharmacia Inc." was deleted.

This editorial change is ACCEPTABLE.

c. The code numbers/letters "KV0404-01- 1 2 3 4 5" were deleted.

This editorial change is ACCEPTABLE.

d. The "Pharmacia" logo was deleted.

This editorial change is ACCEPTABLE.

Conclusions

1. The following identified changes are ACCEPTABLE: 1., 2., 3.a., 5.a., 5.b., 5.c., and 5.d.

2. The following identified changes are UNACCEPTABLE and the firm should be requested to implement the changes identified in the review: 3.b. and 4.

Karen Oliver 09/24/96
Karen Oliver
Regulatory Health Project Manager

cc:
Original 20-287/S-005
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/J.Sieczkowski
HFD-180/S.Fredd

9/24/96

draft: KO/September 19, 1996
r/d Initials: L.Talarico 09/23/96
final: KO/09/24/96/c:\wpwin\karenfil\rev\20287609.0ko

CSO REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-287/S-005

JUN - 6 1997

Name of Drug: Fragmin® (dalteparin sodium injection)

Sponsor: Pharmacia & Upjohn Company

Material Reviewed

Submission Date(s): May 12, 1997

Receipt Date(s): May 14, 1997

Background and Summary Description: Fragmin® (dalteparin sodium injection) is approved for prophylaxis against deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing abdominal surgery who are at risk for thromboembolic complications. Supplement 005, approved September 24, 1996, provided for labeling changes in the DOSAGE AND ADMINISTRATION and the HOW SUPPLIED section of the package insert regarding an autoinjector device, Fragminject™ , available for use with Fragmin syringes. The sponsor submitted Final Printed Labeling (FPL) in response to the September 24, 1996 approval letter.

Review

The FPL, identified as "132041296 Revised March 1997", was compared to the labeling submitted May 16, 1996, identified as "132010496 Revised April 25, 1996" and the revisions requested in the September 24, 1996 approval letter, and they are identical except for the following:

1. The identification numbers were changed.

   This change is ACCEPTABLE.

2. The new Pharmacia & Upjohn tradedress (logo and dynamic frame in the insert heading) was added.

   This change is ACCEPTABLE.

3. The title section was changed

   from: "**Fragmin® (dalteparin sodium injection)**"

"For Subcutaneous use Only"

to: "Fragmin®"- lettering white on black background
"Injection"- lettering white on black background.
"dalteparin sodium injection" - lettering black on white background
"For *Subcutaneous* Use only" - lettering black on white background

This change is UNACCEPTABLE.

4. In the DESCRIPTION section, the first sentence was changed

from: "FRAGMIN® (dalteparin sodium injection)$^{+}$, is a sterile, low molecular weight heparin for injection."

to: "Fragmin Injection contains dalteparin sodium, which is a sterile, low molecular weight heparin."

This change is UNACCEPTABLE.

5. In the CLINICAL PHARMACOLOGY section

a. In the first paragraph, the third sentence, the phrase "factor Xa" was changed to "Factor Xa".

This change is ACCEPTABLE.

b. In the "Pharmacodynamics:" subsection:

(1) In the first sentence, the phrase "anti Factor Xa" was changed to "anti-Factor Xa".

This change is ACCEPTABLE.

(2) In the second sentence, the underlined words in the following sentence were changed

from: "Subcutaneous administration <u>of FRAGMIN doses</u> of 5,000 IU b.i.d. for..."

to: "Subcutaneous administration of doses of 5,000 IU b.i.d. <u>of</u> <u>FRAGMIN</u> for..."

This change is ACCEPTABLE.

c. In the "Pharmacokinetics:" subsection, in the last sentence of the third paragraph, the semicolon after the word "volunteers" was deleted and replaced with a comma to read: "...considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients."

This change is ACCEPTABLE.

d. In the "Clinical Trials:" subsection,

(1) The subsection was changed to a section entitled: "CLINICAL TRIALS".

This change is UNACCEPTABLE. As per 21 CFR 201.56, "Clinical Trials" should be retained as a subsection title.

(2) In the first sentence, the name of the drug "FRAGMIN" was changed to "FRAGMIN Injection".

This change is UNACCEPTABLE.

(3) In the paragraph after "Table 2", in the first sentence, the hyphen in the phrase "once-daily" was deleted to read "once daily".

This change is UNACCEPTABLE. For consistency throughout the text, a hyphen should be retained between the two words "once" and "daily" to read: "once-daily".

(4) In "Table 3", the title of the table was moved from top, left of the table to the top, center of the table, and the "p" value was moved from the bottom, right side of the table to the bottom, left side of the table.

This change is ACCEPTABLE.

6. In the INDICATIONS AND USAGE, CONTRAINDICATIONS, and WARNINGS sections, the in the first sentence of each of the sections, the name of the drug "FRAGMIN" was changed to "FRAGMIN Injection".

This change is UNACCEPTABLE.

7. In the WARNINGS section, the bolding from the following sentence was deleted: "FRAGMIN should be used with extreme caution in patients with history of heparin-induced thrombocytopenia."

This change is UNACCEPTABLE.

8. In the PRECAUTIONS section, the "Pediatric Use:" subsection, the following sentence was changed

from: "Safety and effectiveness in children has not been established."

to: "Safety and effectiveness in pediatric patients have not been established."

This change is ACCEPTABLE.

9. In the ADVERSE REACTIONS section, in the first sentence of the "Hemorrhage:" subsection, the underlined words in the following sentence were changed

from: "The incidence of hemorrhagic complications during FRAGMIN treatment has been low."

to: "The incidence of hemorrhagic complications during treatment with FRAGMIN Injection has been low."

This change is UNACCEPTABLE.

10. In the OVERDOSAGE section, the "Symptoms/Treatment:" subsection, in the first sentence, the name of the drug "FRAGMIN" was changed to "FRAGMIN Injection".

This change is UNACCEPTABLE.

11. In the DOSAGE AND ADMINISTRATION section:

a. In the first paragraph, in the first sentence, the phrase "2500 IU should be administered..." was changed to "2500 IU FRAGMIN Injection should be administered..."

This change is UNACCEPTABLE.

b. In the DOSAGE AND ADMINISTRATION section, the "Administration:" subsection:

(1) The following sentence was changed

from: "An autoinjector, Fragminject, is available for patients to administer daily Fragmin injections."

to: "An autoinjector, FRAGMINJECT™ Autoinjector, is available for patients to administer daily injections of FRAGMIN."

This change is UNACCEPTABLE.

(2) The following sentence was changed

from: "Please see directions accompanying the Fragminject autoinjector."

to: "Please see directions accompanying the FRAGMINJECT."

This change is ACCEPTABLE.

12. After the HOW SUPPLIED section, the following changes were identified:

a. The "+" before "U.S. Patent 4,303,651" was deleted.

This change is ACCEPTABLE.

b. The "Manufactured for" and "Distributed by" were deleted and replaced with:

"Manufactured by:"
"Vetter Pharma-Fertigung"
"Ravensburg, Germany"

"For:"
"Pharmacia & Upjohn Company"
"Kalamazoo, MI 49001, USA"

These changes are ACCEPTABLE.

c. The following numbers were added to the bottom right corner of page 6:
"USA0404-01"

This addition is ACCEPTABLE.

13. A running head, "Fragmin brand of dalteparin sodium injection", has been added at the top of each column of text.

This addition is UNACCEPTABLE.

Conclusion

1. The following changes are ACCEPTABLE: 1., 2., 5.a., 5.b.(1), 5.b.(2), 5.c., 5.d.(4), 8., 11.b(2), 12.a., 12.b., and 12.c.

2. The following changes are UNACCEPTABLE: 3., 4., 5.d.(1-3), 6., 7., 9., 10., 11.a., 11.b.(1), and 13. Changing the proprietary and established names from "Fragmin® (dalteparin sodium injection)" to "Fragmin® Injection dalteparin sodium injection" is unacceptable as it is inconsistent with the cartons and immediate container labels. Further, the name of the drug is used inconsistently throughout the text of the package insert, e.g., "FRAGMIN Injection", "Fragmin® Injection", "Fragmin", "FRAGMIN", "Fragmin® Injection dalteparin sodium injection", and "Fragmin brand of dalteparin sodium injection". These inconsistencies may be misleading and confusing. The firm should be requested to revise the content and format of the drug labeling, including the statement of ingredients, prominence of required label statements, and the statement of identity, such that all drug labeling is consistent and in accordance with 21 CFR 201.10, 201.15, and 201.50.

3. The firm should be requested to submit revised FPL.

Karen Oliver
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

cc:
Original 20-287/S-005
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico 6-6-97
HFD-180/N.Markovic
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
draft: KO/May 27, 1997
r/d init: J.Sieczkowski 06/03/97
r/d init: L.Talarico 06/04/97
final: KO/06/05/97/c:\wpwin\karenfil\rev\20287705.0ko

CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287 (S-005)

CORRESPONDENCE

SEP 24 1996

NDA 20-287/S-005

Pharmacia & Upjohn
Attention: Susan M. Mondabaugh, Ph.D.
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Dear Dr. Mondabaugh:

Please refer to your pending May 16, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (enoxaparin sodium injection).

We have completed our review of your submissions and have the following recommendations regarding the directions for use of the autoinjector titled: "Fragminject™ A patient's guide".

Readability

1. As written, the Patient Guide is at an 11th grade reading level. To reach most of the population, a reading level of sixth or seventh grade is recommended.

2. To make the document more readable, simplify the language and technical terms.

3. Use words of three syllables or fewer.

4. Limit each sentence to 25 words or fewer.

Other Techniques to Enhance Readability

5. Use active not passive verbs.

   a. Example: (page 3.)

      Change from: "To prepare Fragminject for use,..."

      Change to: "Remove the red syringe holder from the main body of the Fragminject by turning it counter-clockwise."

b. Example: (page 8.)

Change from: "After the injection, ..."

Change to: "Turn the safety sleeve counter-clockwise to the locked position."

6. Use words consistently throughout the guide, for example: "doctor" versus "health car provider"; "autoinjector" versus "Fragminject"; "guide" versus "booklet".

7. On page 4:

a. In the "Precaution" section, page 4, identify the action items as "steps" rather than "points".

b. Use an alternative word for "Assembling", such as "Loading".

8. To accommodate users who may have some impaired vision:

a. Print the guide on larger paper.

b. Use a *serif* print of at least 12 points.

c. Make headings larger than the text.

9. Add a table of contents to allow users to find information quickly. Add two new sections: "Resetting Fragminject" and "Troubleshooting".

10. Provide the address and toll-free phone number of the manufacturer for users who may have problems using the device. Incorporate the information into the troubleshooting section.

11. The publisher's address and trademark information is unnecessary and should be deleted, or alternatively, moved to the back of the document, i.e., back cover of the guide.

12. Check that the photos in the guide are clear.

    a. Clarify if the autoinjector body identified in the photo on the page preceding page 1 is the same as the main body of Fragminject. According to step 14., they are two different pieces. Identify the Fragminject "body" in the photo.

    b. Insert a drawing clearly showing the syringe holder and clearly identifying the position used to reset and the other position used for injection.

    c. On page 3, the caption under the first photo should state "arrow shows direction of movement."

    d. On page 4, show the position of the properly inserted syringe before the main body is screwed on.

    e. On page 7, add a diagram over the photo 'showing' the "right angle to the skin surface". Some users may think "right angle" means the "correct angle" rather than a "90^0 angle".

13. Add icons,

    a. On page 2, under the first bullet, add the 'locked' icon as pictured on page 4.

    b. On page 6, include the unlocked icon in the text.

14. Break out the amount of text presented at one time by using white space, highlighting, and bullets.

    a. Example: (page 3)

       In the last sentence, consider changing the word "not" to all capital letters.

    b. Example:

       In the text after the number 4, consider reformatting and rewording to:

"4. Take the red syringe holder in one hand with wider end towards you. Point the grey needle cover end of the syringe into the wider end of the syringe holder."

"Being careful not to press the plunger rod, firmly push the syringe all the way into the holder."

"The grey needle cover will show through the window in the narrow end of the syringe holder when the syringe is correctly in place. The syringe plunger rod will stick out of the wider end."

d. Example (page 4.)

1) The "Precaution" statement should be labeled as a "Warning" rather than a "Precaution".

2) Add a box around the statement to separate if from the rest of the text.

3) Use shorter sentences in the statement.

15. On page 7, change the word "bandaid" as it is a tradename.

Safety and Proper Use

16. The device description needs revision as there is no real description of the device, i.e., spring loaded autoinjector.

17. The indications need to be made clear.

a. Clearly identify the intended audience using the device and the guide.

b. Clearly state when and how often the Fragminject should be used.

18. Include general warning and cautions.

a. Since the device is only to be used with Fragmin, include a brief description of Fragmin.

b. On page 4, break out the statement "Be careful not to press the plunger rod..." into a warning.

c. On page 7, the instructions mention a "little bleeding" which shows a possibility of getting blood on the syringe holder. Provide cleaning instructions.

d. Add a "warning" statement that the user should NOT try to recap the syringe. This should be broken out from the rest of the text.

19. Address the needs of special patient populations in terms of their ability to use the autoinjector, e.g., blind, elderly, arthritic.

Storing and Disposing

20. Under the subheading "Storing the Fragminject", consider adding the following:

a. Store in a dry area at room temperature.

b. Store out of the reach of children.

21. On page 9, the last sentence under "Disposing of the syringe" should be moved and incorporated with the sentence about the syringe disposal container on page 2. This information should be placed up front before the patient uses the device. Add a warning about keeping this container out of the reach of children.

Clarification of Instructions

22. Identify the text about "washing your hands" as the first step to read: "1. To start, wash your hands with soap and water, to prevent infection."

23. Describe, in further detail, the concept of clockwise and counter-clockwise.

24. On page 4, explain that the user will be pushing the syringe against a spring and that this action would be considered "firmly" rather than "gently".

25. If a "click" noise indicates that the syringe is correctly in place, incorporate that information into the instructions.

26. Provide instructions to the user for alternative scenarios, i.e., if the plunger rod is accidentally pressed and the Fragmin is released prematurely; or, the user unlocks/locks the red safety sleeve when screwing the autoinjector on or off which may lead to accidentally pressing the clip and the releasing of Fragmin prematurely.

27. Include a reference to the arrow on the body of the autoinjector, i.e., align the arrow with the locked icon.

28. Include in the instructions that when screwing the syringe holder into the autoinjector, it pushes the grey cap syringe forward.

29. Describe any differences between the actual syringe and the medication syringe in terms of the use with the autoinjector.

30. The text on page 5, except paragraph three, is general information. Group all the general information together. Paragraph three ("Before you inject...") is the action to be taken and should be labeled as step 6.

31. On page 8, include a statement about the user contacting their [doctor or health care provider] if they notice any side effects. Include a list of side effects and any action to relieve those side effects.

32. Include a statement about the following action: when resetting the Fragminject, center the narrow end into the autoinjector to correctly push the spring back.

33. The statement on page 9, "When you have pushed the syringe holder..." is confusing. State that the user should continue to push the syringe holder while screwing it clockwise. Include a statement that the syringe holder should be screwed in all the way until it is tight to ensure the Fragminject has been resent.

User Testing

Test the device and its labeling on an appropriate target group to assess the user's ability to understand and follow the directions.

If you have any questions, please contact:

Karen Oliver
Regulatory Health Project Manager
(301) 443-0487

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and
Research

cc:
Original NDA 20-287/S-005
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/J.Sieczkowski
HFD-180/L.Talarico
HFZ-480/V.Nakayama
HFD-820/Yuan Yuan Chiu (only for CMC related issues)

drafted: KO/September 19, 1996
r/d Initials: L.Talarico 09/23/96
r/d Initials: S.Fredd 09/24/96
final: KO/09/24/96/c:\wpwin\nda\20287609.1ko

K Oliver 09/24/96

GENERAL CORRESPONDENCE

SF 9/24/96

APPEARS THIS WAY
ON ORIGINAL