

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
20-430/S-003**

**Administrative Documents**

**Division of Gastrointestinal & Coagulation Drug Products  
CONSUMER SAFETY OFFICER REVIEW**

**Application Number:** NDA 20-430/S-003

**Name of Drug:** Orgaran® (danaparoid sodium) Injection

**Sponsor:** Organon Inc.

**Material Reviewed**

**Submission Date(s):** August 25, 2000

**Receipt Date(s):** August 28, 2000

**Background and Summary Description:** Supplement 003 provides for the following changes: (1) in the CLINICAL PHARMACOLOGY section, the addition of a subsection titled "Special Populations", with three sub-subsections titled "Geriatrics", "Pediatrics", and "Hepatic Insufficiency"; (2) in the PRECAUTIONS section, additional information in the "Geriatric Use" subsection; and (3) in the DOSAGE AND ADMINISTRATION section, the addition of a subsection titled "Use in Geriatrics".

**Review**

**PACKAGE INSERT**

The draft package insert text, identified as "5310150 6/2000" was compared to the FPL, identified as "5310150 10/98 19", in annual report Y-003 and an amendment to Y-003, submitted March 7 and May 9, 2000, respectively. The text of package inserts are identical except for the following:

1. The identification numbers have changed.

**This change is ACCEPTABLE.**

2. In the DESCRIPTION section, in the second paragraph, the third sentence, the phrase "ORGARAN® Injection" has been changed to "ORGARAN®".

**This change is ACCEPTABLE.**

3. In the CLINICAL PHARMACOLOGY section, the "Pharmacodynamics" subsection, the format of the sub-subsections has been changed

from:

to:

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

Effect on Coagulation Factors

**This change, implemented throughout the package inert, is ACCEPTABLE.**

4. In the CLINICAL PHARMACOLOGY section, the "Pharmacodynamics" subsection, the "Measurements of Hemostasis" has been changed from \_\_\_\_\_ to a sub-subsection title.

**This change is ACCEPTABLE.**

5. In the CLINICAL PHARMACOLOGY section, the "Pharmacodynamics" subsection, the "Measurements of Hemostasis" sub-subsection, the phrase ' \_\_\_\_\_ ' has been changed to "ORGARAN<sup>®</sup>".

**This change is ACCEPTABLE.**

6. In the CLINICAL PHARMACOLOGY section, a new subsection was added titled "Special Populations". The subsection contains 6 sub-subsections titled "Geriatrics", "Pediatrics", "Race", "Hepatic Insufficiency", "Renal Insufficiency", and "Drug-Drug Interactions". The subsection information reads as follows:

## **Special Populations**

### Geriatrics

There are insufficient pharmacokinetic data to determine if the absorption, distribution, and elimination of ORGARAN<sup>®</sup> (danaparoid sodium) for Injection are different in elderly ( $\geq 65$  years) subjects when compared with younger subjects.

### Pediatrics

The safety and efficacy of ORGARAN<sup>®</sup> in pediatric patients have not been established.

### Race

There is no information to determine the effect of race on the pharmacokinetics of ORGARAN<sup>®</sup>.

### Hepatic Insufficiency

No formal studies were conducted to evaluate the effect of hepatic disease of disposition of ORGARAN<sup>®</sup>.

### Renal Insufficiency

No formal studies were conducted to evaluate the effect of renal disease on the disposition of ORGARAN<sup>®</sup> although ORGARAN<sup>®</sup> is mainly eliminated in the kidneys. In patients with severely impaired renal function, the half-life of elimination of plasma anti-Xa activity may be prolonged, therefore, careful monitoring of such patients is recommended (see PRECAUTIONS).

Drug-Drug Interactions

In clinical studies for the prophylaxis of DVT, no significant drug interactions have been noted in the following drugs: digoxin, cloxacillin, ticarcillin, chlorthalidone, and pentobarbital (see PRECAUTIONS).

ORGARAN® should be used with caution in patients receiving oral anticoagulants and/or platelet inhibitors. Monitoring of anticoagulants by Prothrombin Time and Thrombotest is unreliable within 5 hours after ORGARAN® administration (see PRECAUTIONS).

**The information contained in this new subsection was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and it is ACCEPTABLE.**

7. In the CLINICAL PHARMACOLOGY section:
  - a. The " " subsection title has been changed to "Clinical Studies".  
**This change ACCEPTABLE.**
  - b. In the first paragraph, the first sentence, the comma after the word "trial" has been deleted.  
**This deletion is ACCEPTABLE.**
  - c. In the second paragraph, the first sentence, the comma after the word "trial" has been deleted.  
**This change is ACCEPTABLE.**
  
8. In the CONTRAINDICATIONS section, the first sentence, the italics were removed from the phrase "in vitro" and the "I" in the word "Injection" was changed from a capital to a small letter.  
**These changes are UNACCEPTABLE.** The phrases should read "*in vitro*" and "ORGARAN® Injection".

9. In the PRECAUTIONS section, the "General" subsection, in the first sentence, the bolding was deleted from the phrase "(see DOSAGE AND ADMINISTRATION)".

**This is UNACCEPTABLE.** The phrase should be revised to read: "(see **DOSAGE AND ADMINISTRATION**)". Further, for all the reference phrases throughout the text, the section title should be bolded.

10. In the PRECAUTIONS section, the "Teratogenic Effects-Pregnancy Category B" subsection, in the first sentence, the phrase ' was changed to "ORGARAN<sup>®</sup>".

**This change ACCEPTABLE.**

11. In the PRECAUTIONS section, a new subsection, titled "Geriatric Use", has been added. The subsection reads as follows:

#### **Geriatric Use**

Of the total number of patients undergoing elective hip replacement surgery who received ORGARAN<sup>®</sup> (danaparoid sodium) Injection in clinical studies, 62% (397/645 patients) were  $\geq 65$  years and 22% (141/645 patients) were  $\geq 75$  years old. No overall differences in safety and effectiveness of ORGARAN<sup>®</sup> were observed between elderly ( $\geq 65$  years) subjects and younger subjects. Other reported clinical experience with ORGARAN<sup>®</sup> has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals to ORGARAN<sup>®</sup> cannot be ruled out.

ORGARAN<sup>®</sup> is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

**The information in this subsection was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and it is ACCEPTABLE.**

12. In the ADVERSE REACTIONS section, in the first table, the title of the table was changed from capital and small letters, to all capital letters.

**This change is UNACCEPTABLE.** For consistency throughout the text, the title of the table should be changed to read as follows:

**Blood Loss and Transfusions  
DVT and PE Prophylaxis for Orthopedic Hip Surgery  
All Patients Treated**

13. In the DOSAGE AND ADMINISTRATION section, in the "Usual Adult Dosage" subsection:
- a. The underline and colon (at the end of the title) were deleted from the subsection title.

**This deletion is ACCEPTABLE.** The subsection title reads as follows:

**Usual Adult Dosage**

- b. In the first sentence, the phrase " " was changed to "1 to 4 hours".

**This change is ACCEPTABLE.**

14. In the DOSAGE AND ADMINISTRATION section, a "Use in Geriatrics" subsection has been added to read as follows:

**Use in Geriatrics**

No overall difference in safety and effectiveness of ORGARAN<sup>®</sup> (danaparoid sodium) Injection were observed in elderly ( $\geq 65$  years) patients when compared with younger ( $< 65$  years) patients undergoing elective hip replacement surgery. Therefore, no dosage adjustments are recommended in elderly patients.

**This additional subsection was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and it is UNACCEPTABLE.** The subsection should be revised to read as follows:

**Use in Geriatrics**

No overall differences in safety and effectiveness of ORGARAN® (danaparoid sodium) Injection were observed in patients  $\geq 65$  years when compared with patients  $< 65$  years undergoing elective hip replacement surgery. No dosage adjustments are recommended in elderly patients.

15. In the DOSAGE AND ADMINISTRATION section, the "Administration" subsection, the underline and colon (at the end of the title) were deleted from the subsection title.

**This deletion is ACCEPTABLE.** The subsection title reads as follows:

**Administration**

16. In the HOW SUPPLIED section, in the "Storage" subsection:

- a. In the colon after the subsection title was deleted. The subsection title reads as follows:

**Storage**

**This change is ACCEPTABLE.**

- b. The storage statements have been changed

from:

to:

- Ampules should be stored at controlled room temperature, 2-30°C (36-86°F).
- Syringes should be stored refrigerated, 2-8°C (36-46°F).
- Protect from light.

**These changes were reviewed by the CHEMISTRY REVIEWER,  
Dr. Ali Al-Hakim, and they are ACCEPTABLE.**

16. After the HOW SUPPLIED section, the “**R** only” phrase has been deleted and replaced with the phrase “ only”.

**This is UNACCEPTABLE.** The “**R** only” phrase should be re-instated.

18. After the HOW SUPPLIED section, the format of the logo has changed

from:

to:

Organon Inc.



West Orange, N.J. 07052

**This change is ACCEPTABLE.**

19. After the HOW SUPPLIED section, below (and to the left of the logo) the words “Printed in USA” have been deleted.

**This deletion is ACCEPTABLE.**

**Conclusions**

1. The following changes are ACCEPTABLE: 1., 2., 3., 4., 5., 6., 7.a., 7.b., 7.c., 10., 11., 13.a., 13.b., 15., 16.a., 16.b., 18, and 19.
2. The following changes are UNACCEPTABLE: 8., 9., 12., 14., and 17.

/S/ 6/26/01

---

Karen Oliver, RN, MSN  
Regulatory Health Project Manager

/S/ 6/26/01

---

Lilia Talarico, M.D.  
Division Director

cc:

Original NDA 20-430/S-003

HFD-180/Div. Files

HFD-180/L.Talarico

HFD-180/A.Farrell

HFD-180/K.Oliver

R/D init: R.He 06/25/01

R/D init: K.Robie-Suh 06/25/01

R/D init: L.Talarico 06/25/01

draft: KO/December 28, 2000

final: KO/06/26/01

CSO REVIEW