

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

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

**Medical Review(s)**

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG  
PRODUCTS MEDICAL OFFICER'S REVIEW**

NDA: 20-430/SE8-003

Sponsor: ORGANON, INC  
375 Mt. Pleasant Avenue  
West Orange, NJ 07052

Drug name: **Orgaran** (danaparoid sodium)

Route of Administration: Subcutaneous Injection

Indication: Prophylaxis of post-operative DVT, which may lead to PE, in patients  
undergoing elective hip replacement surgery

Submission: Geriatric labeling Supplement

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Reviewer: Ruyi He, M.D.

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## EXECUTIVE SUMMARY

The results from reanalysis of the data from clinical studies (9 studies for safety and 2 studies for efficacy), show no differences in the safety and effectiveness of Orgaran in patients  $\geq 65$  years versus patients  $< 65$  years administered Orgaran for the approved indication of prophylaxis of post-operative DVT, which may lead to PE, in patients undergoing elective hip replacement surgery. Also, Orgaran does not appear to cause any specific hazard in patients  $\geq 65$  years versus patients  $< 65$  years that would require special monitoring or dosage adjustment.

I recommend that the Geriatric Use of Orgaran for the approved indication of prophylaxis of post-operative DVT, which may lead to PE, in patients undergoing elective hip replacement surgery be approved.

The following section should be added to the Package Insert under **DOSAGE AND ADMINISTRATION**.

**Use in Geriatrics:** No overall differences in safety and effectiveness of Orgaran 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 geriatric population.

The reviewer agrees with the sponsor's proposed labeling changes under **CLINICAL PHARMACOLOGY: Special Populations** (see also Biopharmaceutics Review). The proposed labeling under **PRECAUTIONS: Geriatric Use** is acceptable. The reviewer does not recommend any other changes for the remainder of the Orgaran Labeling.

Efficacy data from the two pivotal studies (Studies 85140 and 004-023) included in the original NDA 20-430 were reanalyzed for patients  $\geq 65$  years and patients  $< 65$  years. A total of 396 patients  $\geq 65$  years (204 in the Orgaran, 71 in the placebo and 121 in the Warfarin group) and 196 patients  $< 65$  years (93 in the Orgaran, 27 in the placebo and 76 in the Warfarin group) enrolled in these two studies. More female patients than male patients were enrolled in the Orgaran group for both studies (78% and 62%). In both studies, results for patients  $\geq 65$  years treated with Orgaran were consistent with results for all Orgaran®-treated patients. This finding was expected since patients  $\geq 65$  years comprised the majority of the total ITT population (73% and 64%) in these two studies.

In Study 85140, patients  $\geq 65$  years in the Orgaran® treatment group had greater incidences of proximal, distal, and overall DVT compared with patients  $< 65$  years; similarly, this finding was observed in the control (placebo) group. In Study 004-023, the incidences of DVT (proximal, distal, and overall) were similar in patients  $\geq 65$  years and patients  $< 65$  years treated with Orgaran.

In comparison with control groups (placebo or warfarin), patients  $\geq 65$  years treated with Orgaran had a significant reduction of overall DVT rates in both studies ( $p \leq 0.001$  in Study 85140 and  $p \leq 0.05$  in Study 004-023). Patients  $< 65$  years treated with Orgaran had

a significant reduction of overall DVT rates in comparison with placebo ( $P < 0.01$ ), however, patients  $< 65$  years treated with Orgaran did not reach a significant reduction of overall DVT rates in comparison with warfarin group. It maybe secondary to limited number of patients  $< 65$  years enrolled in the study. The relative reduction rate of DVT incidence treated by Orgaran is numerically higher in the patients  $< 65$  years group than in the patients  $\geq 65$  years group.

The data reviewed showed no clinically meaningful differences in the safety of Orgaran in patients  $\geq 65$  years versus patients  $< 65$  years. In clinical studies of Orgaran three patients  $\geq 65$  years died during study (one during Orgaran treatment and two in the post-treatment period) and were considered unrelated to Orgaran. There were no treatment-emergent or post-treatment deaths in patients  $< 65$  years treated with Orgaran.

The incidences of non-fatal SAEs and discontinuations due to AEs were similar for patients  $\geq 65$  years and patients  $< 65$  years treated with Orgaran. The most frequently reported AEs by Orgaran treated patients of both age groups were pain, fever, nausea, constipation, and injection site pain. The incidence of injection site pain and nausea were similar in the two age groups, and the incidences of pain, fever, and constipation were greater in patients  $\geq 65$  years. Adverse events that occurred in patients  $\geq 65$  years but were not reported by patients  $< 65$  years treated with Orgaran included edema, asthenia, dizziness, confusion, urinary retention, and increased cough. In Orgaran-treated patients, AEs that occurred in patients  $< 65$  years, but were not observed in patients  $\geq 65$  years included abdominal pain, dyspepsia, and hypochromic anemia.

In the Orgaran treatment group, mean postoperative blood loss was similar for patients  $\geq 65$  years and patients  $< 65$  years of both sexes. The mean volume of blood transfused was not affected by the age of patients treated with Orgaran.

A review of available data from post-marketing safety surveillance did not indicate any differences in the safety profile of commercially-available Orgaran in patients  $\geq 65$  years compared with patients  $< 65$  years.

APPEARS THIS WAY  
ON ORIGINAL

## 1 INTRODUCTION:

Orgaran® (danaparoid sodium) Injection is a sterile, glycosaminoglycuronan antithrombotic agent approved for marketing in the United States for the prophylaxis of post-operative deep venous thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing elective hip replacement surgery.

In this submission, the sponsor submitted a geriatric labeling supplement for the approved indication mentioned above. The sponsor conducted analyses to determine the differences in the pharmacokinetics, efficacy and safety of Orgaran in patients  $\geq 65$  years old versus patients  $< 65$  years old. This submission summarizes the results of these analyses.

## 2 COMPARISON OF THE PHARMACOKINETICS (AGE $\geq 65$ YEARS VERSUS $< 65$ YEARS)

The differences in the pharmacokinetics of Orgaran® in patients  $\geq 65$  years old versus patients  $< 65$  years old are presented and discussed in some detail in the FDA Biopharmaceutics Review. Briefly: Four Phase I clinical pharmacology studies conducted in 44 healthy patients 55-76 years of age were completed and included in the original NDA 20-430. These studies did not provide a sufficient number of patients to determine whether there was a difference in the pharmacokinetics of Orgaran in patients  $\geq 65$  years compared with patients  $< 65$  years. Based on a population pharmacokinetic analysis, the covariates of age, sex, and weight were not found to be important for Orgaran.

A review of the literature revealed one publication which concluded that the pharmacokinetics of Orgaran® were not influenced by age.

## 3 COMPARISON OF EFFICACY (AGE $\geq 65$ YEARS VERSUS $< 65$ YEARS)

Efficacy data applicable to patients  $\geq 65$  years of age are summarized from the Integrated Summary of Effectiveness (ISE) data of New Drug Application (NDA) 20-430. The population examined includes patients from two Phase III controlled clinical studies that were completed and included in the original NDA. No additional clinical efficacy studies were included in this submission.

### 3.1 Method

Two controlled studies (Studies 85140 and 004-023) support the approved indication mentioned above. For both studies, the incidences of proximal, distal, and overall DVT in patients  $\geq 65$  years and patients  $< 65$  years were compared between treatment groups by using a two-sided Fisher's Exact Test. Statistical significance was defined as  $p \leq 0.05$ . These data were analyzed for the "Intent-to-Treat" (ITT) population, which includes patients who took at least one dose of study medication, underwent the protocol-specified surgery, and had at least one efficacy evaluation. A total of 12 patients were excluded after randomization because no study drug was taken. A total of 80 patients (34 from the

Orgaran group and 46 from the warfarin group) were excluded from the ITT in Study 004-023 and 22 patients (11 in each group) were excluded from ITT in Study 85140 because venography was not performed. More warfarin-treated patients failed to undergo venogram, however, no significant differences were noted between treatment groups at any of the study centers (medical officer's review for NDA 20-430, page 11-12, 37-39).

### 3.2 Results

A total of 396 patients  $\geq 65$  years and 196 patients  $< 65$  years were treated in Studies 85140 and 004-023.

The table below summarizes the number of patients  $\geq 65$  years and the number of patients  $< 65$  years in the ITT population included in the efficacy analyses for Studies 85140 and 004-023.

**Table 1: Number of Patients  $\geq 65$  Years and Number of Patients  $< 65$  Years in the Efficacy Analyses by Treatment (ITT Population)**

Study	Number of patients					
	$< 65$ years			$\geq 65$ years		
	Orgaran®	Placebo	Warfarin	Orgaran®	Placebo	Warfarin
85140	25	27		73	71	
004-023	68		76	131		121
Total	93	27	76	204	71	121

Sponsor's table, copied from Vol. 2, page 10

#### 3.2.1 Study 85140

Study 85140, conducted in The Netherlands, was a randomized, placebo-controlled, double-blind, multicenter study. The study medications, Orgaran® 750 anti-Xa units (0.6 mL) b.i.d. and placebo 0.6 mL b.i.d., were to be administered subcutaneously for 10 days or until discharge from the hospital.

Most of the ITT population (73%; 144 of 196 patients) were  $\geq 65$  years. There were no significant differences between the patients  $\geq 65$  years and patients  $< 65$  years with regard to demographic characteristics (other than age) and duration of treatment. The mean duration of treatment was  $10 \pm 1$  days. More female patients than male patients were enrolled in this study for both study groups and for both patients  $\geq 65$  years and patients  $< 65$  years.

The demographic characteristics and duration of treatment between the patients  $\geq 65$  years and patients  $< 65$  years are summarized in the table below.

**Table 2: Demographic Characteristics and duration of treatment of Patients  $\geq 65$  Years and Patients  $< 65$  Years by Treatment in Study 85140**

Demographic characteristic	$< 65$ years		$\geq 65$ years	
	Orgaran (N=25)	Placebo (N=27)	Orgaran (N=73)	Placebo (N=71)
<b>Sex (n, %)</b>				
Female	20 (80)	18 (67)	57 (78)	54 (76)
Male	5 (20)	9 (33)	16 (22)	17 (24)
<b>Body weight (kg)</b>				
n	25	27	73	71
Mean $\pm$ SD	72 $\pm$ 15	71 $\pm$ 11	72 $\pm$ 12	72 $\pm$ 12
Median	72	71	72	71
Range				
<b>Height (cm)</b>				
n	25	27	73	71
Mean $\pm$ SD	166 $\pm$ 10	168 $\pm$ 8	165 $\pm$ 9	166 $\pm$ 8
Median	163	167	164	166
Range				
<b>Number of days treated</b>				
Mean $\pm$ SD	10 $\pm$ 1	10 $\pm$ 1	10 $\pm$ 1	10 $\pm$ 1
Median	10	10	10	10
Range				

**Incidence of DVT**

The patients  $\geq 65$  years treated with Orgaran had an 11% greater incidence of proximal DVT, an 8% greater incidence of distal DVT, and a 10% greater incidence of overall DVT compared with patients  $< 65$  years treated with Orgaran (table 3). In the placebo group, patients  $\geq 65$  years had a 16% greater incidence of proximal DVT, 21% greater incidence of distal DVT, and a 18% greater incidence of overall DVT compared with patients  $< 65$  years (table 3).

In comparison with patients  $\geq 65$  years treated with placebo, patients  $\geq 65$  years treated with Orgaran achieved a statistically significant reduction in the incidences of proximal ( $p \leq 0.01$ ), distal ( $p \leq 0.001$ ), and overall DVT ( $p \leq 0.001$ ). The response observed in patients  $\geq 65$  years treated with Orgaran was consistent with the response observed in all Orgaran treated patients. However, the response observed in patients  $\geq 65$  years treated with Orgaran was less than the response observed in patients  $< 65$  years treated with Orgaran (71% versus 82% of relative reduction). This may be secondary to limited number of patients  $< 65$  years enrolled in the Orgaran group (N=25).

Incidences of DVT in patients  $\geq 65$  years and patients  $< 65$  years by treatment in Study 85140 (ITT population) are summarized in the table below:

**Table 3: Incidence of DVT in Patients  $\geq 65$  Years and Patients  $< 65$  Years by Treatment in Study 85140 (ITT Population)**

Location of DVT	Number (%) of patients					
	$< 65$ years		$\geq 65$ years		All patients (Package Insert)	
	Orgaran <sup>®</sup> (N=25)	Placebo (N=27)	Orgaran <sup>®</sup> (N=73)	Placebo (N=71)	Orgaran <sup>®</sup> (N=98)	Placebo (N=98)
Proximal n (%)	0	4 (15)	8 (11)**	22 (31)	8 (8)***	26 (27)
Distal n (%)	2 (8)*	10 (37)	12 (16)***	41 (58)	14 (14)***	51 (52)
Overall n (%)	2 (8)**	12 (44)	13 (18)***	44 (62)	15 (15)***	56 (57)
Relative reduction <sup>a</sup>	82%		71%		74%	

Sponsor's table, copied from Vol. 2, page 12.

- <sup>a</sup> Relative reduction in DVT incidence for Orgaran<sup>®</sup> compared with placebo = [(placebo incidence - Orgaran<sup>®</sup> incidence)/placebo incidence] x 100
- \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$  vs. placebo: for by-age analyses, two-sided Fisher's Exact Test; for All Patients analysis from Package Insert, Cochran-Mantel-Haenszel test.

Note: The overall number of patients with DVT may not equal the sum of proximal plus distal DVT because a patient could have had both a proximal and a distal DVT.

### 3.2.2 Study 004-023

Study 004-023, conducted in the United States, was a randomized, active-controlled, assessor-blinded, multicenter study. The study medications, Orgaran<sup>®</sup> 750 anti-Xa units (0.6mL) b.i.d, and warfarin sodium (oral daily dose adjusted to each patient's prothrombin time [PT] or international normalized ratio [INR]), were to be administered subcutaneously for up to 6 days or until discharge from the hospital.

#### Demographics

A total of 12 patients were excluded after randomization because no study drug was taken. A total of 80 patients (34 from the Orgaran group and 46 from the warfarin group) were excluded from the ITT in Study 004-023 and 22 patients (11 in each group) were excluded from ITT in Study 85140 because venography was not performed. More warfarin-treated patients failed to undergo venogram; however, no significant differences were noted between treatment groups at any of the study centers (medical officer's review for NDA 20-430, page 11-12, 37-39).

Most patients (64%; 252 of 396) were  $\geq 65$  years. The race and weight were similar between the patients  $\geq 65$  years and patients  $< 65$  years treated with Orgaran<sup>®</sup>, but the

two age groups were somewhat different with respect to sex and weight. A total of 62% of patients  $\geq 65$  years treated with Orgaran<sup>®</sup> were female and 38% were male. In comparison, 41% of patients  $< 65$  years treated with Orgaran<sup>®</sup> were female and 59% were male. The mean weight for patients  $\geq 65$  years treated with Orgaran<sup>®</sup> was  $76 \pm 18$  kg and for patients  $< 65$  years treated with Orgaran<sup>®</sup> was  $84 \pm 17$  kg.

Demographic characteristics of patients  $\geq 65$  years and patients  $< 65$  years by treatment in Study 004-023 (ITT Population) are summarized in the table below.

**Table 4 Demographic Characteristics of Patients  $\geq 65$  Years and Patients  $< 65$  Years by Treatment in Study 004-023 (ITT Population)**

Demographic Characteristic	$< 65$ years		$\geq 65$ years	
	Orgaran N=68	warfarin N=76	Orgaran N=131	Warfarin N=121
Sex (n, %)				
Female	28 (41)	28 (37)	81 (62)	67 (55)
Male	40 (59)	48 (63)	50 (38)	54 (45)
Race (n, %)				
Caucasian	67 (99)	67 (88)	125 (95)	117 (97)
Other	1 (2)	9 (12)	6 (5)	4 (3)
Body weight (kg)				
n	68	70	131	116
Mean $\pm$ SD	$84 \pm 17$	$86 \pm 19$	$76 \pm 18$	$77 \pm 16$
Median	84	86	73	75
Range				
Height (cm)				
n	68	70	130	115
Mean $\pm$ SD	$172 \pm 10$	$172 \pm 11$	$167 \pm 11$	$169 \pm 11$
Median	173	173	166	170
Range				

#### Duration of Treatment

Patients received Orgaran<sup>®</sup> 750 anti-Xa units (0.6 mL) b.i.d, subcutaneously or oral warfarin adjusted to each patient's PT or INR for  $7 \pm 1$  days.

The mean duration of treatment for patients  $\geq 65$  years and patients  $< 65$  years treated with Orgaran is summarized in the table below.

**Table 5 Duration of Treatment for Patients  $\geq 65$  Years and Patients  $< 65$  Years by Treatment in Study 004-023 (ITT Population)**

Number of days treated	$< 65$ years		$\geq 65$ years	
	Orgaran N=68	Warfarin N=76	Orgaran N=131	Warfarin N=121
Mean $\pm$ SD	7 $\pm$ 1	7 $\pm$ 1	7 $\pm$ 1	7 $\pm$ 1
Median	7	7	8	7
Range				

**Incidence of DVT**

The incidences of proximal DVT (2%), distal DVT (13%), and overall DVT (14%) in patients  $\geq 65$  years treated with Orgaran, were similar to those observed in patients  $< 65$  years treated with Orgaran (0%, 16%, and 16%, respectively). Also, the results observed in patients  $\geq 65$  years treated with Orgaran were consistent with the results observed in all Orgaran-treated patients. In this study, patients  $\geq 65$  years comprised 64% of the total ITT population.

The incidences of DVT in patients  $\geq 65$  years and patients  $< 65$  years by treatment in Study 004-023 (ITT Population) are summarized in the table below.

**Table 6: Incidence of DVT in Patients  $\geq 65$  Years and Patients  $< 65$  Years by Treatment in Study 004-023 (ITT Population)**

Location of DVT	$< 65$ years		$\geq 65$ years		All patients	
	Orgaran <sup>®</sup> N=68	warfarin N=76	Orgaran <sup>®</sup> N=131	Warfarin N=121	Orgaran <sup>®</sup> N=199	Warfarin N=197
Proximal n (%)	0	2 (3)	3 (2)	6 (5)	3 (2)	8 (4)
Distal n (%)	11 (16)	23 (30)	17 (13)	26 (22)	28 (14)**	49 (25)
Overall n (%)	11 (16)	23 (30)	18 (14)*	30 (25)	29 (15)**	53 (27)
Relative reduction <sup>a</sup>	47%		44%		44%	

<sup>a</sup> Relative reduction in DVT incidence for Orgaran<sup>®</sup> compared with warfarin = [(warfarin incidence - Orgaran<sup>®</sup> incidence)/warfarin incidence] x 100

\*  $p < 0.05$ , \*\*  $p < 0.01$  vs. warfarin: for by-age analyses, two-sided Fisher's Exact Test; for All Patients analysis from Package Inset, Cochran-Mantel-Haenszel test.

Note: The overall number of patients with DVT may not equal the sum of proximal + distal DVT because a patient could have had both a proximal and a distal DVT.

### 3.3 Summary of Efficacy

- Efficacy data from the two pivotal studies (Studies 85140 and 004-023) included in the original NDA 20-430 were reanalyzed for patients  $\geq 65$  years and patients  $< 65$  years. More female patients than male patients were enrolled in the Orgaran group for both studies (78% and 62%). In both studies, results for patients  $\geq 65$  years treated with Orgaran were consistent with results for all Orgaran®-treated patients. This finding was expected since patients  $\geq 65$  years comprised the majority of the total ITT population (73% and 64%) in these two studies.

In Study 85140, patients  $\geq 65$  years in the Orgaran® treatment group had greater incidences of proximal, distal, and overall DVT compared with patients  $< 65$  years; similarly, this finding was observed in the control (placebo) group. In Study 004-023, the incidences of DVT (proximal, distal, and overall) were similar in patients  $\geq 65$  years and patients  $< 65$  years treated with Orgaran.

In comparison with control groups (placebo or warfarin), patients  $\geq 65$  years treated with Orgaran had a significant reduction of overall DVT rates in both studies ( $p \leq 0.001$  in Study 85140 and  $p \leq 0.05$  in Study 004-023). Patients  $< 65$  years treated with Orgaran had a significant reduction of overall DVT rates in comparison with placebo ( $P < 0.01$ ), however, patients  $< 65$  years treated with Orgaran did not reach a significant reduction of overall DVT rates in comparison with warfarin group. It maybe secondary to limited number of patients  $< 65$  years enrolled in the study. The relative reduction rate of DVT incidence treated by orgaran is numerically higher in the patients  $< 65$  years group than in the patients  $\geq 65$  years group.

In conclusion, Orgaran was effective in prophylaxis of post-operative DVT, which may lead to PE, in both patients  $\geq 65$  years and  $< 65$  years undergoing elective hip replacement surgery, based on these two studies.

## 4 COMPARISON OF SAFETY RESULTS (AGE $\geq 65$ YEARS VERSUS $< 65$ YEARS)

### 4.1 Methods

#### 4.1.1 Data from clinical studies

Adverse event (AE) data applicable to patients  $\geq 65$  years of age are summarized from the Integrated Summary of Safety Data (ISS) of New Drug Application (NDA) 20-430 and subsequent safety updates. The population examined includes patients from nine Phase II or Phase III clinical studies that were completed and included in the original NDA for the approved indication of prophylaxis of post-operative DVT, which may lead to PE, in patients undergoing elective hip replacement surgery.

New analyses of AEs for patients  $\geq 65$  years compared with patients  $< 65$  years are

presented below. These data were analyzed for the All-Patients-Treated population, which includes all patients who received at least one dose of study medication.

The new analyses of AE data include an analysis of treatment-emergent AEs that occurred after the first dose of study medication up to the end of the protocol-specified treatment period of the study and an analysis of post-treatment AEs that occurred anytime after the protocol-specified treatment period of the study.

#### **4.1.2 Post-marketing Safety Surveillance Report with This Submission**

The post-marketing safety surveillance database for Orgaran® was evaluated from December 1992 through December 31, 1999, and all spontaneous reports of serious adverse events (SAEs)/AEs for patients  $\geq 65$  years and patients  $< 65$  years were reviewed. It was not possible to determine a denominator for the patients  $\geq 65$  years and patients  $< 65$  years. However, as of December 31, 1999, a total of            ampoules and syringes (            total dosage units) of Orgaran® had been sold in the US and            ampoules had been sold outside the US (            total dosage units worldwide).

#### **4.1.3 Periodic Safety Reports**

The sponsor submitted a period safety report on February 5, 2001 which covered the period from December 1, 1999 through December 23, 2000. All spontaneous reports in this period were reviewed.

### **4.2 Safety Results**

#### **4.2.1 Data from Clinical Studies**

A total of 1191 patients were included in the nine clinical studies for the DVT and PE prophylaxis in patients undergoing elective hip replacement surgery. There were 645 Orgaran-treated patients, 135 treated by placebo, 243 treated by warfarin and 168 patients treated by other (heparin or Dextran). In each treatment group, the majority of patients were  $\geq 65$  years and the percentages of patients  $\geq 65$  years and patients  $< 65$  years were similar.

The table below presents the number and percentage of patients  $\geq 65$  years and patients  $< 65$  years by treatment.





**Table 9: Demographic Characteristics of Patients  $\geq 65$  Years and Patients  $< 65$  Years in the Integrated Database for DVT and PE Prophylaxis for Elective Hip Replacement Surgery by Treatment (All-Patients-Treated Population)**

Age Group and Demographic Parameter	Treatment			
	Orgaran <sup>3</sup> (N=645)	Placebo (N=135)	Warfann (N=243)	Other (N=168)
<b>&lt;65 years</b>	<b>N=248</b>	<b>N=44</b>	<b>N=95</b>	<b>N=64</b>
Sex (n, %)				
Female	123 (49.6%)	29 (65.9%)	34 (35.8%)	47 (73.4%)
Male	125 (50.4%)	15 (34.1%)	61 (64.2%)	17 (26.6%)
Race (n, %) <sup>a</sup>				
Caucasian	108 (43.5%)	0	84 (88.4%)	6 (9.4%)
Other	9 (3.6%)	0	11 (11.6%)	0
Unknown	131 (52.8%)	44 (100.0%)	0	58 (90.6%)
Body weight (kg)				
Mean $\pm$ SD	77 $\pm$ 16	71 $\pm$ 10	86 $\pm$ 19 (N=87)	72 $\pm$ 12
Median	75	71	86	72
Range	46-132	53-99	54-136	49-96
Height (cm)				
Mean $\pm$ SD	169 $\pm$ 10 (N=247)	168 $\pm$ 9	172 $\pm$ 11 (N=87)	167 $\pm$ 7
Median	169	167	173	166
Range	145-196	150-187	135-193	152-185
<b><math>\geq 65</math> years</b>	<b>N=397</b>	<b>N=91</b>	<b>N=148</b>	<b>N=104</b>
Sex (n, %)				
Female	259 (65.2%)	68 (74.7%)	85 (57.4%)	71 (68.3%)
Male	138 (34.8%)	23 (25.3%)	63 (42.6%)	33 (31.7%)
Race (n, %) <sup>a</sup>				
Caucasian	178 (44.8%)	0	144 (97.3%)	6 (5.8%)
Other	12 (3.0%)	0	4 (2.7%)	0
Unknown	207 (52.1%)	91 (100.0%)	0	98 (94.2%)
Body weight (kg)				
Mean $\pm$ SD	73 $\pm$ 14 (N=394)	71 $\pm$ 12	76 $\pm$ 15 (N=141)	68 $\pm$ 15 (N=102)
Median	72	70	75	65
Range	41-127	45-100	41-126	40-124
Height (cm)				
Mean $\pm$ SD	166 $\pm$ 10 (N=391)	165 $\pm$ 8	168 $\pm$ 11 (N=140)	162 $\pm$ 9 (N=102)
Median	165	165	169	162
Range	137-193	148-187	127-196	127-182

Source data: Appendix A, Tables 5, 6, 9, 10, 13, 14, 17, and 18

Note: Percentages may not equal 100% due to rounding.

<sup>a</sup> Race was not reported for the 109 Orgaran<sup>3</sup>-treated patients and 109 placebo-treated patients in Study 85140.

## Adverse Events

### Death

A total of 3 deaths occurred during or after participation in the nine clinical studies. One patient died during the treatment period and two patients died in the post-treatment period. No patients <65 years died during and after the treatment period. These 3 deaths are presented as following:

- A 77-year old female patient who received Orgaran® for five days died of chronic cardiac arrhythmia. This death was considered unrelated to Orgaran by investigator.
- A 75-year old female died of colorectal cancer approximately 3 months after her last dose of Orgaran® (relationship to Orgaran® was not available from the investigator's report).
- A 69-year old female died of pulmonary embolism approximately five weeks after the final dose of study medication (considered unrelated to Orgaran® by investigator).

### Non-Fatal Serious Adverse Events

The overall incidence of non-fatal serious adverse events (SAEs) in Orgaran-treated patients  $\geq$  65 years (3%) was similar to this incidence in Orgaran-treated patients < 65 years (2%).

A total of 15 non-fatal serious adverse events were reported in 12 of 397 (3%) Orgaran-treated patients  $\geq$  65 years. Four of these non-fatal SAEs were considered to be possibly related to treatment with Orgaran by investigators. These non-fatal SAEs were suspected angina pectoris, acute gastric dilatation and chondrocalcinosis. A total of 5 non-fatal serious adverse events were reported in 5 of 248 (2%) Orgaran-treated patients < 65 years. None of these non-fatal SAEs were considered to be related to treatment with Orgaran by investigators.

The table below summarized the non-fatal SAEs in patients treated with Orgaran by age groups.

**Table 10: Summary of Non-fatal SAEs in Patients  $\geq$  65 Years and Patients < 65 years treated with Orgaran**

Non-fatal SAE	Patient $\geq$ 65 y	Patient <65 y	Relationship to Orgaran
Allergic injection site reaction		32/F	Unknown
Dislocated left hip prosthesis	68/F	53/F	No
Abdominal pain	70/F		Unknown
Septicemia	80/F		No
Suspected angina pectoris	68/F		Possible
Nausea	70/F		Unknown
Acute gastric dilatation	77/M		Possible
thrombocytopenia		53/F	Unlikely
Acute gastric dilatation	77/M		Possible
Edema of left foot	71/F		Unlikely
Chondrocalcinosis	73/F		Possible
Hallucinations	71/F		No
Right-sided weakness/stroke	81/F		No
Aphasia	81/F		No
Suspected pulmonary embolus		61/F	No
Shortness of breath		61/F	Unknown
pulmonary embolus	74/F, 71/F, 75/F		No
<b>Total</b>	<b>15</b>	<b>5</b>	<b>4 possible</b>

Reviewer's table, summarized from Vol. 3, page 61 to 64. Appendix A: table 23.

### Discontinuations Due to Adverse Events

The percentages of Orgaran®-treated patients  $\geq 65$  years and patients  $< 65$  years who discontinued study medication due to an AE were similar (2.4% and 2.3%, respectively). A total of 9 Orgaran-treated patients  $\geq 65$  years withdrew from the study due to adverse events. Each adverse event leading to the discontinuation occurred in one patient each. These adverse events included fever; Right-sided "weakness"/"stroke" and aphasia; hypotension; angina pectoris; healing abnormal (wound oozing); jaundice from hemolytic anemia; hallucinations; confusion; and paralysis and neuropathy. The AEs leading to the discontinuation of Orgaran®-treated patients  $< 65$  years were injection site pain (n = 3), injection site reaction (n = 1), allergic reaction (n = 1), and fever (n = 1).

The table below summarizes the discontinuation from study medication due to adverse events by age groups and treatment groups.

**Table 11: Discontinuations from Study Medication Due to Adverse Events for Patients  $\geq 65$  Years and Patients  $< 65$  Years by Treatment (All-Patients-Treated Population)**

Age Group	Treatment											
	Orgaran <sup>1</sup> (N=645)			Placebo (N=135)			Warfann (N=243)			Other (N=168)		
	N	n	%	N	n	%	N	n	%	N	n	%
<65 years	248	6	2.4	44	2	4.5	95	0	0	64	5	7.8
$\geq 65$ years	397	9	2.3	91	1	1.1	148	2	1.4	104	1	1.0
$\geq 65$ to $< 75$ years	256	6	2.3	50	1	2.0	92	1	1.1	58	0	0
$\geq 75$ years	141	3	2.1	41	0	0	56	1	1.8	46	1	2.2

Source data: Appendix A, Table 24

Note: N and n for patients  $\geq 65$  years is the sum of the data for patients  $\geq 65$  to  $< 75$  years plus data for patients  $\geq 75$  years. A patient who withdrew from treatment for multiple AEs is counted only once.

### Adverse Events by COSTART Preferred Term

The table below summarizes treatment-emergent AEs (by COSTART Preferred Term) that occurred in at least 2% of patients in the nine clinical studies by treatment group and age.

**Table 12: Summary treatment-emergent AEs that occurred in  $\geq 2\%$  of patients in the nine clinical studies by treatment group and age.**

Adverse Events	Orgaran n (%)		Placebo n (%)	
	$\geq 65$ years n=397	$< 65$ years n=248	$\geq 65$ years n=91	$< 65$ years n=44
Pain	129 (32.5)	67 (27)	0	0
Fever	95 (23.9)	48 (19.4)	1 (1.1)	0
Nausea	59 (14.9)	33 (13.3)	1 (1.1)	2 (4.5)
Constipation	50 (12.6)	23 (9.3)	0	0
Injection site pain	31 (7.8)	18 (7.3)	3 (3.3)	1 (2.3)
Rash	24 (6)	7 (2.8)	0	0
Pruritus	20 (5)	5 (5)	0	1 (2.3)
Peripheral edema	17 (4.3)	0	0	0
Vomiting	14 (3.5)	5 (2)	1 (1.1)	2 (4.5)
Edema	14 (3.5)	0	0	0
Asthenia	12 (3)	0	0	0
Headache	12 (3)	5 (2)	1 (1.1)	0
Dizziness	12 (3)	0	0	0
Confusion	11 (2.8)	0	0	0
Insomnia	11 (2.8)	9 (3.6)	0	0
Urinary retention	10 (2.5)	0	0	0
Joint disorder	9 (2.3)	8 (3.2)	0	0
Anemia	8 (2)	11 (4.4)	3 (3.3)	0
Cough	8 (2)	0	0	0
Abdominal pain	0	5 (2)	0	0
Despepsia	0	5 (2)	0	0

Reviewer's table, summarized from Vol. 3 page 19 to 21.

The most frequently reported AEs in Orgaran-treated patients  $\geq 65$  years and patients  $< 65$  years were (in order of decreasing incidence) pain, fever, nausea, constipation, and injection site pain. The incidences of these adverse events in Orgaran-treated patients were higher than the incidences in placebo-treated patients (both age groups). The incidences of injection site pain, nausea and pruritus were similar in patients  $\geq 65$  years and patients  $< 65$  years treated with Orgaran. The incidences of pain, fever, and constipation, rash, edema and dizziness in Orgaran-treated patients were greater in patients  $\geq 65$  years compared with patients  $< 65$  years. In placebo-treated patients, there were no incidents of pain, constipation or rash in either age category.

In Orgaran-treated patients, AEs that occurred in patients  $\geq 65$  years, but were not reported by patients  $< 65$  years included (in order of decreasing incidence in Orgaran-treated patients  $\geq 65$  years) peripheral edema, edema, asthenia, dizziness, confusion, urinary retention, and increased cough. In placebo-treated patients, there were no incidents of each of these AEs in either age category.

In Orgaran-treated patients, AEs that occurred in patients  $< 65$  years, but were not observed in patients  $\geq 65$  years included (in order of decreasing incidence in Orgaran-treated patients  $< 65$  years) abdominal pain and dyspepsia. In placebo-treated patients, there were no incidents of each of these three AEs in either age category.

## Bleeding Events

The table below summarizes the bleeding events that occurred in nine clinical studies by treatment groups and ages.

**Table 13: Summary the bleeding events occurred in clinical studies by treatment groups and ages**

Type of Bleeding	Orgaran n (%)		Placebo n (%)	
	≥65 years n=397	<65 years n=248	≥65 years n=91	<65 years n=44
Intraoperative Blood Loss	330 (83)	210 (85)	36 (40)	22 (50)
Postoperative Blood Loss	343 (86)	226 (91)	89 (98)	43 (98)
Transfusion	325 (82)	206 (83)	73 (80)	37 (84)

Reviewer's table, summarized from Vol. 3 page 23 to 25, table 8 to 10.

There was no significant difference in the incidence of bleeding events between patients  $\geq 65$  years and patients  $< 65$  years, although there was a higher incidence of intraoperative blood loss in Orgaran-treated patients than placebo-treated patients.

The mean (SD) intraoperative blood loss in Orgaran-treated males  $\geq 65$  years was 763 (504) mL and in Orgaran-treated males  $< 65$  years, intraoperative blood loss was 908 (634) mL. Since the standard deviations were so large, it was different to make a meaningful comparison of the mean values.

The postoperative blood loss and mean volume of blood transfused were not affected by the age of the patients, or by the treatment administered. In the Orgaran-treatment group, the mean (SD) units of packed red blood cells (PRBCs) administered to males  $\geq 65$  years was 2.3 (1.5) and to males  $< 65$  years was 2.6 (2.1). The mean (SD) units of PRBCs administered to females  $\geq 65$  years was 2.7 (1.5) and to females  $< 65$  years was 2.9 (2.5).

### 4.2.2 Post-marketing Safety Surveillance

A total of 51 spontaneous reports were received from December, 1992 through December 31, 1999. The following is a summary of the cases in patients  $\geq 65$  years compared with patients  $< 65$  years.

There were 24 total cases in patients  $\geq 65$  years and 22 total cases in patients  $< 65$  years; the age of patients for five cases was unknown.

There were seven reports identifying patients who had died (two patients  $\geq 65$  years, four patients  $< 65$  years, and one patient of unknown age). For the two patients  $\geq 65$  years, the AE(s) were: a 75-year old male receiving Orgaran for "thrombocytopenia" experienced "granulocytopenia" and an 81-year old female receiving Orgaran for an unknown

indication experience "thrombocytopenia". For the four patients <65 years, the adverse event(s) were:

- a 30-year old female receiving Orgaran for "HIT" (heparin-induced thrombocytopenia) who experienced "vaginal bleeding" and "placental disorder";
- a 45-year old female who experienced "skin exfoliation" and "skin necrosis";
- a 53-year old male who developed "sepsis"
- a 60-year old male receiving Orgaran for "thrombocytopenia" who experienced "thrombosis" and thrombocytopenia."

The female patient of unknown age who was receiving Orgaran for "coronary artery bypass" was "kidney failure".

There are no significant safety issues based on post-market safety surveillance report.

#### **4.2.3 Periodic Safety Reports and AERS DataMart Search**

The sponsor submitted a period safety report on February 5, 2001 which covered the period from December 1, 1999 through December 23, 2000. There were five 15-Day Reports submitted during the above period. There were 16 spontaneous reports from AERS DataMart search from December 1, 1999 through March 2001. The 5 cases reported by the sponsor were included in the 16 spontaneous reports from AERS DataMart search. A total of 11 of 16 patients were 65 years or older (65-88), 3 patients were less than 65 years (53, 56 and 63) and ages of 2 patients were unknown.

Adverse events reported included hematoma, renal failure, myocardial infarction, neutrophilia, drug ineffective and melaena et al. No specific pattern can be summarized from these reports. There are no new or unlabeled significant safety issues based on these post-market safety spontaneous reports.

#### **4.3 Safety Summary**

The data reviewed showed no clinically meaningful differences in the safety of Orgaran in patients  $\geq 65$  years versus patients <65 years. In clinical studies of Orgaran three patients  $\geq 65$  years died during study (one during Orgaran treatment and two in the post-treatment period) and were considered unrelated to Orgaran. There were no treatment-emergent or post-treatment deaths in patients <65 years treated with Orgaran.

The incidences of non-fatal SAEs and discontinuations due to AEs were similar for patients  $\geq 65$  years and patients <65 years treated with Orgaran. The most frequently reported AEs by Orgaran treated patients of both age groups were pain, fever, nausea, constipation, and injection site pain. The incidence of injection site pain and nausea were similar in the two age groups, and the incidences of pain, fever, and constipation were greater in patients  $\geq 65$  years. Adverse events that occurred in patients  $\geq 65$  years but were not reported by patients <65 years treated with Orgaran included edema, asthenia, dizziness, confusion, urinary retention, and increased cough. In Orgaran-treated patients, AEs that occurred in patients <65 years, but were not observed in patients  $\geq 65$  years

included abdominal pain, dyspepsia, and hypochromic anemia.

In the Orgaran treatment group, mean postoperative blood loss was similar for patients  $\geq 65$  years and patients  $< 65$  years of both sexes. The mean volume of blood transfused was not affected by the age of patients treated with Orgaran.

A review of available data from post-marketing safety surveillance did not indicate any differences in the safety profile of commercially-available Orgaran in patients  $\geq 65$  years compared with patients  $< 65$  years.

## 5 CONCLUSIONS AND RECOMMENDATIONS

Based on the results from reanalysis of the data from clinical studies (9 studies for safety and 2 studies for efficacy), there are no differences in the safety and effectiveness of Orgaran in patients  $\geq 65$  years versus patients  $< 65$  years administered Orgaran for the approved indication of prophylaxis of post-operative DVT, which may lead to PE, in patients undergoing elective hip replacement surgery. Also, Orgaran does not appear to cause any specific hazard in patients  $\geq 65$  years versus patients  $< 65$  years that would require special monitoring or dosage adjustment.

I recommend that the Geriatric Use of Orgaran for the approved indication of prophylaxis of post-operative DVT, which may lead to PE, in patients undergoing elective hip replacement surgery be approved.

The following section should be added to the Package Insert under **DOSAGE AND ADMINISTRATION. Use in Geriatrics:** No overall differences in safety and effectiveness of Orgaran 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 geriatric population.

The reviewer agrees with the sponsor's proposed labeling changes under **CLINICAL PHARMACOLOGY: Special Populations** (see also Biopharmaceutics Review). The proposed labeling under **PRECAUTIONS: Geriatric Use** is acceptable. The reviewer does not recommend any other changes for the remainder of the Orgaran Labeling.

The recommendations should be communicated to the sponsor.

/S/ 6/20/01

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Ruyi He, MD

CC: