Duramed Clinical Study, Continued

Table 3

Discontinued Patients
Pivotal Study 366

Patient #	Treatment	Approx. Exposure*	Reason
031	Placebo	Completed week 10 Weeks 2 & 3: 2 x 0.625 mg Weeks 4-10: 1 x 0.625 mg	Withdrawn by principal investigator (PI) due to thoracic pulmonary compliance, high blood pressure and headache
048	Active	Completed week 3 2 x 0.625 mg	Dropped by study management due to missed visit and missed doses
053	Placebo	Completed week 1 1 x 0.625 mg	Dropped by study management due to missed visit and inability to continue study
060	Placebo	Completed Week 2 1 x 0.625 mg	Patient withdrew at her request (job schedule)
061	Placebo	3 days 1 x 0.625 mg	Patient withdrew at her request because treatment made her nauseous
074	Active	Completed Week 10 2 x 0.625 mg	Withdrawn by PI due to non-serious adverse events (melancholia and emotional discomfort)
076	Active	2 days 1 x 0.625 mg	Withdrawn by PI due to non-serious adverse events (visual difficulty, feeling odd, abdominal cramps)
091	Placebo	Completed Week 5 2 x 0.625 mg	Patient withdrew at her request – no reason provided
102	Placebo	Completed Week 10 2 x 0.625 mg	Withdrawn by PI due to a non-serious adverse event (very tender/painful cyst in her lower left quadrant of her left breast)
130	Active	Completed Week 5 2 x 0.625 mg	Withdrawn by PI due to a non-serious adverse event

*see study medication data listing 16.2.5.3.1, NDA Volume 13 for complete exposure

Continued on next page

Duramed Clinical Study, Continued

Study Event Incidence

Treatment emergent adverse events were reported by 111 (93%) of patients enrolled in the study. Of the patients who received synthetic conjugated estrogens, 68 (94%) reported at least one adverse event and of those who received placebo, 43 (90%) reported at least one adverse event. The most commonly reported adverse events, reported by greater than 30% of all patients were Headache (68%), Insomnia (44%), Asthenia (37%), Nervousness (33%), Paresthesia (33%), and Depression (32%). The most commonly reported events, reported by greater than 30% of all patients who received synthetic conjugated estrogens were Headache (68%), Insomnia (42%), Asthenia (33%), and Paresthesia (33%). The most commonly reported events, reported by > 30% of all patients who received placebo were Headache (67%), Insomnia (48%), Asthenia (42%), Nervousness (42%), Depression (38%), Myalgia (31%), and Paresthesia (31%). There were not any deaths or serious adverse events reported during this study.

Table 4 on the following page summarizes all adverse events that occurred in greater than 5% of the patients in either treatments group. The statistical significance of any difference in occurrence rates between treatment groups was not determined.

Table 5 on page 11 presents the actual number of adverse events that occurred in greater than 5 % of the patients in either treatment group. Again, the statistical significance of any differences between groups was not determined.

Relationship of Adverse Events to Treatments

Although statistical analyses were not performed, the incidence of adverse events in the synthetic conjugated estrogens group appears to be similar, or lower than that in the placebo group. There appears to be a slightly higher incidence of Urogenital System Adverse Events in the patients who received synthetic conjugated estrogens than in the placebo group. Thirty (30) of the 72 patients (42%) who received synthetic conjugated estrogens reported 56 adverse events. Eleven (11) of the 48 patients (23%) who received placebo reported 27 adverse events. Twenty-one (21) patients (29%) who were treated with synthetic conjugated estrogens reported 28 occurrences of Breast Pain compared to 7 patients (15%) who received placebo and reported 12 occurrences of Breast Pain. Likewise, 10 patients (14%) who received synthetic conjugated estrogens reported 18 occurrences of Metrorrhagia, while 3 patients (6%) who received placebo reported 9 occurrences of Metrorrhagia. These are adverse events that are typically expected with estrogen replacement therapy.

Continued on next page

Duramed Clinical Study, Continued

Relationship of Adverse Events to Treatments – continued

Table 6 on page 12 presents a summary of the intensity and relationship to drug of adverse events that occurred in the synthetic conjugated estrogen group. Table 7 on page 5 presents a summary of the intensity and relationship to drug of adverse events that occurred in the placebo group The adverse event categories selected for presentation in these tables represent any adverse event that occurred in greater than 5% of patients in any treatment group.

As expected, the relationship to treatment of the adverse events typically associated with estrogen replacement therapy (Breast Pain, Metrorrhagia, Nausea and Peripheral Edema) was generally classified as "possible" or "highly probable" for both treatment groups.

The only other Adverse Events occurring in greater than 5% of either treatment group, a large portion of which were classified as "possible" or "highly probable" were Abdominal Pain and Flatulence. Although statistical significance was not determined, these events appear to occur at similar rates in both treatment groups.

The distribution of intensity of adverse events also appears to be similar between treatment groups.

Continued on next page

Duramed Clinical Study, Continued

Table 4

Number (%) of Patients with Adverse Events with a Greater than 5% Occurrence Rate By Body System and Treatment Group
Pivotal Study 366

Body System Adverse Event	Synthetic Conjugated Estrogen N (%)	Placebo N (%)	Total N (%)
# Patients Who Received Medication	72 (100)	48 (100)	120 (100)
# Patients With Adverse Events	68 (94)	43 (90)	111 (93)
# Patients Without Any Adverse Events	4 (6)	5 (10)	9 (8)
Body As A Whole	**60 (83)**	**39 (81)**	**99 (83)**
Abdominal Pain	20 (28)	11 (23)	31 (26)
Asthenia	24 (33)	20 (42)	44 (37)
Back Pain	10 (14)	6 (13)	16 (13)
Fever	1 (1)	3 (6)	4 (3)
Headache	49 (68)	32 (67)	81 (68)
Infection	10 (14)	5 (10)	15 (13)
Pain	8 (11)	9 (19)	17 (14)
Cardiovascular System	**16 (22)**	**15 (31)**	**31 (26)**
Palpitation	15 (21)	13 (27)	28 (23)
Digestive System	**30 (42)**	**25 (52)**	**55 (46)**
Constipation	4 (6)	2 (4)	6 (5)
Diarrhea	4 (6)	0 (0)	4 (3)
Dyspepsia	7 (10)	3 (6)	10 (8)
Flatulence	21 (29)	14 (29)	35 (29)
Nausea	13 (18)	9 (19)	22 (18)
Vomiting	5 (7)	1 (2)	6 (5)
Metabolic and Nutritional	**11 (15)**	**9 (19)**	**20 (17)**
Peripheral Edema	7 (10)	6 (13)	13 (11)
Musculoskeletal System	**24 (33)**	**16 (33)**	**40 (33)**
Arthralgia	18 (25)	13 (27)	31 (26)
Myalgia	20 (28)	15 (31)	35 (29)
Nervous System	**55 (76)**	**35 (73)**	**90 (75)**
Depression	20 (28)	18 (38)	38 (32)
Dizziness	8 (11)	5 (10)	13 (11)
Hypertonia	4 (6)	0 (0)	4 (3)
Insomnia	30 (42)	23 (48)	53 (44)
Leg Cramps	7 (10)	3 (6)	10 (8)
Nervousness	20 (28)	20 (42)	40 (33)
Paresthesia	24 (33)	15 (31)	39 (33)
Vertigo	12 (17)	12 (25)	24 (20)
Respiratory System	**18 (25)**	**11 (23)**	**29 (24)**
Cough Increased	4 (6)	1 (2)	5 (4)
Pharyngitis	6 (8)	4 (8)	10 (8)
Rhinitis	6 (8)	7(15)	13 (11)
Skin and Appendages	**9 (13)**	**5 (10)**	**14 (12)**
Rash	3 (4)	3 (6)	6 (5)
Special Senses	**3 (4)**	**6 (13)**	**9 (8)**
Urogenital System	**30 (42)**	**11 (23)**	**41 (34)**
Breast Pain	21 (29)	7 (15)	28 (23)
Dysmenorrhea	4 (6)	3 (6)	7 (6)
Metrorrhagia	10 (14)	3 (6)	13 (11)

Source: Table 14.3.1.1, NDA Volume 7

Duramed Clinical Study, Continued.

Table 5

Number of Adverse Events That Occurred in Greater than 5% of Patients
by Treatment Group and Body System
Pivotal Study 366

Body System Adverse Event	Synthetic Conjugated Estrogens N (%)*	Placebo N (%)*	Total N (%)*
Number of Adverse Events	748 (100)	514 (100)	1262 (100)
Body as a Whole	**239 (32)**	**190 (37)**	**429 (34)**
Abdominal Pain	28 (4)	14 (3)	42 (3)
Asthenia	35 (5)	30 (6)	65 (5)
Back Pain	20 (3)	10 (2)	30 (2)
Fever	1 (0)	3 (1)	4 (0)
Headache	122 (16)	102 (20)	244 (18)
Infection	15 (2)	5 (1)	20 (2)
Pain	8 (1)	19 (4)	27 (2)
Cardiovascular System	**26 (3)**	**22 (4)**	**48 (4)**
Palpitation	24 (3)	18 (4)	42 (3)
Digestive System	**82 (11)**	**40 (8)**	**122 (10)**
Constipation	6 (1)	3 (1)	9 (1)
Diarrhea	4 (1)	0 (0)	4 (0)
Dyspepsia	13 (2)	3 (1)	16 (1)
Flatulence	30 (4)	19 (4)	49 (4)
Nausea	18 (2)	11 (2)	29 (2)
Vomiting	11 (1)	1 (0)	12 (1)
Metabolic and Nutritional	**16 (2)**	**14 (3)**	**30 (2)**
Peripheral Edema	11 (1)	10 (2)	21 (2)
Musculoskeletal System	**53 (7)**	**40 (8)**	**93 (7)**
Arthralgia	24 (3)	13 (3)	37 (3)
Myalgia	28 (4)	23 (4)	51 (4)
Nervous System	**228 (30)**	**140 (27)**	**368 (29)**
Depression	29 (4)	27 (5)	56 (4)
Dizziness	10 (1)	5 (1)	15 (1)
Hypertonia	4 (1)	0 (0)	4 (0)
Insomnia	47 (6)	29 (6)	76 (6)
Leg Cramps	31 (4)	3 (1)	34 (3)
Nervousness	30 (4)	24 (5)	54 (4)
Paresthesia	40 (5)	24 (5)	64 (5)
Vertigo	20 (3)	13 (3)	33 (3)
Respiratory System	**31 (4)**	**25 (5)**	**56 (4)**
Cough Increased	4 (1)	1 (0)	5 (0)
Pharyngitis	7 (1)	7 (1)	14 (1)
Rhinitis	11 (1)	14 (3)	25 (2)
Skin and Appendages	**13 (2)**	**9 (2)**	**22 (2)**
Rash	3 (0)	3 (1)	6 (0)
Special Senses	**4 (1)**	**6 (1)**	**10 (1)**
Urogenital System	**56 (7)**	**27 (5)**	**83 (7)**
Breast Pain	28 (4)	12 (2)	40 (3)
Dysmenorrhea	4 (1)	3 (1)	7 (1)
Metrorrhagia	18 (2)	9 (2)	27 (2)

*Percent of total number of Adverse Events Source: Table 14.3.1.2, NDA Volume 7

Duramed Clinical Study, Continued

Table 6

Severity and Relationship to Drug of Adverse Events Occurring in Greater than 5% of any Treatment Group; Synthetic Conjugated Estrogens
Pivotal Study 366

Adverse Event	Number of		Intensity			Relationship to Drug			
	Patients	Events	Mild	Moderate	Severe	Un-known	Un-related	Possible	Highly Probable
Abdominal Pain	20	28	21	6	1	0	4	11	13
Arthralgia	18	24	11	7	6	0	24	0	0
Asthenia	24	35	16	16	3	0	28	3	4
Back Pain	10	20	3	17	0	0	20	0	0
Breast Pain	21	28	21	5	2	0	3	3	22
Constipation	4	6	0	6	0	0	6	0	0
Cough Increased	4	4	2	1	1	0	4	0	0
Depression	20	29	12	16	1	0	23	6	0
Diarrhea	4	4	3	0	1	0	4	0	0
Dizziness	8	10	7	2	1	0	6	4	0
Dys-menorrhea	4	4	2	2	0	0	0	2	2
Dyspepsia	7	13	3	9	1	0	3	10	0
Fever	1	1	1	0	0	0	1	0	0
Flatulence	21	30	19	10	1	0	5	14	11
Headache	49	122	71	28	23	0	69	53	0
Hypertonia	4	4	2	2	0	0	4	0	0
Infection	10	15	1	7	7	0	15	0	0
Insomnia	30	47	27	11	9	0	46	1	0
Leg Cramps	7	31	16	11	4	0	5	26	0
Metrorrhagia	10	18	15	3	0	0	1	4	13
Myalgia	20	28	12	11	5	0	28	0	0
Nausea	13	18	13	4	1	0	2	13	3
Nervousness	20	30	20	7	3	0	30	0	0
Pain	8	8	4	4	0	0	7	0	1
Palpitation	15	24	14	8	2	0	24	0	0
Paresthesia	24	40	30	9	1	9	31	0	0
Peripheral Edema	7	11	3	8	0	0	0	6	5
Pharyngitis	6	7	2	3	2	0	7	0	0
Rash	3	3	2	0	1	0	3	0	0
Rhinitis	6	11	2	5	4	0	11	0	0
Vertigo	12	20	13	6	1	0	13	7	0
Vomiting	5	11	5	3	3	0	0	11	0

Source: Table 14.3.1.3.1, NDA Volume 7

Duramed Clinical Study, Continued

Table 7

Severity and Relationship to Drug of Adverse Events Occurring in Greater than 5% of any Treatment Group; Placebo

Adverse Event	Number of		Intensity			Relationship to Drug			
	Patients	Events	Mild	Moderate	Severe	Un-known	Un-related	Possible	Highly Probable
Abdominal Pain	11	14	11	2	1	0	2	5	7
Arthralgia	13	13	5	3	5	0	13	0	0
Asthenia	20	30	18	10	2	0	27	2	1
Back Pain	6	10	0	8	2	0	10	0	0
Breast Pain	7	12	10	1	1	0	0	0	12
Constipation	2	3	3	0	0	0	3	0	0
Cough Increased	1	1	0	1	0	0	1	0	0
Depression	18	27	8	12	7	0	19	8	0
Diarrhea	0	0	0	0	0	0	0	0	0
Dizziness	5	5	3	2	0	0	3	2	0
Dys-menorrhea	3	3	2	1	0	0	2	1	0
Dyspepsia	3	3	2	1	0	0	2	1	0
Fever	3	3	2	1	0	0	3	0	0
Flatulence	14	19	13	5	1	0	1	8	10
Headache	32	102	43	43	16	0	61	41	0
Hypertonia	0	0	0	0	0	0	0	0	0
Infection	5	5	2	3	0	0	5	0	0
Insomnia	23	29	9	14	6	0	29	0	0
Leg Cramps	3	3	1	1	1	0	1	2	0
Metrorrhagia	3	9	6	3	0	0	0	3	6
Myalgia	15	23	9	9	5	0	22	1	0
Nausea	9	11	8	3	0	0	3	6	2
Nervousness	20	24	10	9	5	0	24	0	0
Pain	9	19	8	9	2	0	18	1	0
Palpitation	13	18	13	5	0	0	18	0	0
Paresthesia	15	24	12	10	2	4	19	1	0
Peripheral Edema	6	10	7	2	1	0	0	9	1
Pharyngitis	4	7	5	1	1	0	7	0	0
Rash	3	3	2	1	0	1	2	0	0
Rhinitis	7	14	8	4	2	0	14	0	0
Vertigo	12	13	10	3	0	0	9	4	0
Vomiting	1	1	0	1	0	0	0	1	0

Source: Table 14.3.1.3.1, NDA Volume 7

Continued on next page

Duramed Clinical Study, Continued

Clinical Evaluations

In Duramed's pivotal study 366 routine laboratory tests and a physical and gynecological examination were conducted at screening and at each patients final visit (i.e., at the end of the 12 weeks of treatment or at discontinuation). Mammography was done at screening and vital signs were conducted at all visits except week 10.

Clinical Laboratory Findings

Table 7 presents the statistically significant changes from screening to final visit in laboratory parameters. There were only two statistically significant laboratory value shifts in the synthetic conjugated estrogen treatment group when data from 65 patients were examined as a whole. Albumin and glucose were the two mean laboratory values that shifted from screening to final visit in the active treatment group. The magnitude of the statistically significant changes from screening to final visit was very small and not thought to be clinically significant. The placebo treatment group (n=39) had no significant laboratory shifts from screening to final visit for any of the laboratory values examined in this study.

The by-subject review of clinically notable laboratory abnormalities are presented in Table 9 (Hematology) Table 10 (Biochemistry) and Table 11 (Liver Function And Lipid Values). Seven (7) of the 120 patients (6%) enrolled into the study listed one or more clinically significant abnormalities. Overall, zero (0) of the 120 patients enrolled into the study discontinued due to abnormal laboratory measurements.

Table 8

Statistically Significant Changes from Screening to Final Visit in Laboratory Parameters

Laboratory Parameter (Units)	N	Treatment	Change from Screening to Final Visit (mean ± SD)		Chi-Square Value
			Screening	Final Visit	
Albumin (g/dL)	68	Active	4.35 ± 0.28	4.18 ± 0.34	9.091*
	44	Placebo	4.40 ± 0.29	4.28 ± 0.22	2.250
Glucose (mg/dL)	68	Active	83.46 ± 8.16	88.54 ± 14.96	7.111*
	44	Placebo	86.79 ± 7.69	87.36 ± 10.16	5.000

*= Chi-Square value is from Stuart-Maxwell's or McNemar's test with *<0.05
Source Data: Section 14, Table 14.3.4.8, NDA Volume 7

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Duramed Clinical Study, Continued

Table 9

Clinically Notable Abnormal Laboratory Values
Hematology

Patient	Site (Location)	Formulation	Period	Hematocrit (%), Significance	Hemoglobin (g/dL), Significance
103	3 (Phoenix, AZ)	Active	Screen	35.4	11.7
			Final Visit	28.9 LY+	9.5 LY+

Source Data: Section 14, Table 14.3.4.1.2 and Appendix 16.2.8.2.2, NDA Volume 7
LY+ = Below Normal Range, Clinically Significant, Principle Investigator interpretation: clinically significant.

Table 10

Clinically Notable Abnormal Laboratory Values
Biochemistry

Patient	Site (Location)	Formulation	Laboratory Test (Units)	Period	Results, Significance
015	1 (Lincoln, NE)	Placebo	Alkaline (U/L)	Screen	91
				Final Visit	109 HYR
117	1 (Lincoln, NE)	Active	Uric Acid (mg/dL)	Screen	5.7
				Final Visit	6.7 HYR
				Recheck	7.0 HY+
120	2 (Omaha, NE)	Active	Potassium (mEq/L)	Screen	5.6 HYR
				Recheck	4.2
				Final Visit	4.5
120	2 (Omaha, NE)	Active	Urea (mg/dL)	Screen	21 HN
				Final Visit	25 HYR
				Recheck	24 HYR
121	2 (Omaha, NE)	Active	Potassium (mEq/L)	Screen	5.4 HYR
				Recheck Final Visit	4.1
					5.3 HN
122	2 (Omaha, NE)	Active	Glucose (ng/dL)	Screen	82
				Final Visit	6 LYR
				Recheck	91

Source Data: Section 14, Tables 14.3.4.5.1 to 14.3.4.5.4 and Appendices 16.2.8.1.1 to 16.2.8.1.4, NDA Volume 7
HN = Above Normal Range, Not Clinically Significant
HYR = Above Normal Range, Clinically Significant, Recheck Requested.
HY+ = Above Normal Range, Clinically Significant, Principle Investigator interpretation: clinically significant.
LYR = Below Normal Range, Clinically Significant, Recheck Requested.
*YR = Out of Range, Clinically Significant, Recheck Requested.

Continued on next page

Duramed Clinical Study, Continued

Table 11

Clinically Notable Abnormal Laboratory Values
Liver Function And Lipid Values

Patient	Site (Location)	Formulation	Laboratory Test (Units)	Period	Results, Significance	
003	1 (Lincoln, NE)	Active	Triglyceride (mg/dL)	Screen	101	
				Final Visit	319	HYR
				Recheck	220	
117	1 (Lincoln, NE)	Active	Cholesterol (mg/dL)	Screen	279	HN
				Final Visit	341	HYR
				Recheck	310	HY+
117	1 (Lincoln, NE)	Active	Triglyceride (mg/dL)	Screen	344	HYR
				Recheck	234	
				Recheck	377	HYR
				Final Visit	471	HYR
				Recheck	906	HY+

Source Data: Section 14, Tables 14.3.4.9.1 and 14.3.4.9.2 and Appendices 16.2.8.1.2 and 16.2.8.1.3. NDA Vol. 7
HYR = Above Normal Range, Clinically Significant, Recheck Requested.
HN = Above Normal Range, Not Clinically Significant
HY+ = Above Normal Range, Clinically Significant, Principle Investigator interpretation: clinically significant.

Physical Examination Findings

Physical and gynecological exams were conducted on all patients at screening and at the final visit There were no clinically significant changes in physical or gynecological examinations from screening.

Systolic and diastolic blood pressure, pulse rate and weight were recorded at screening, baseline, visits 1, 2, 3, 4, 5, 6, 7 and final visit or as soon as possible after discontinuation. In general, there were few noticeable changes in vital sign measurements. No patterns were seen across treatment groups and the average changes were of small magnitude. These minor fluctuations were not considered to be clinically meaningful by the principle investigators.

Ancillary Studies

Overview

Duramed conducted five (5) pharmacokinetic studies to determine the relative bioavailability of Cenestin™ to Premarin® with respect to plasma concentrations of conjugated and unconjugated estrone and equilin. The identity of these studies is presented in Table 12 below.

Table 12

Pharmacokinetic Studies of Cenestin™ Tablets

Study #	Dose	Conditions	Clinical Date
CN054	2 x 0.625 mg	Fasted – Pilot	July 1993
BN038	2 x 0.625 mg	Fasted	October 1993 – January 1994
930125	2 x 0.625 mg	Fed	November 1993
BN037	1 x 1.25 mg	Fasted	May – September 1995
941817	1 x 1.25 mg	Fed/Fasted	October – December 1995

Extent of Exposure

Each of the five (5) pharmacokinetic studies was a single-dose crossover study that determined the relative bioavailability of Cenestin™ and Premarin®. The exposure difference between studies was in the number of periods. This information is presented in the Table 13 below.

Table 13

Extent of Exposure to Cenestin™ Tablets

Study #	# Subjects	Dose	# Periods (Drug Products)
CN054	12	2 x 0.625 mg	3 (2 research formulations, 1 Premarin®)
BN038	36	2 x 0.625 mg	4 (2 Cenestin™, 2 Premarin®)
930125	18	2 x 0.625 mg	2 (1 Cenestin™, 1Premarin®)
BN037	36	1 x 1.25 mg	4 (2 Cenestin™, 2 Premarin®)
941817	24	1 x 1.25 mg	4 (2 Cenestin™, 2 Premarin®)

Continued on next page

Ancillary Studies, Continued

Demographic Characteristics

The inclusion/exclusion criteria were similar for all 5 studies. The demographic characteristics at baseline are summarized in Table 14. To be included in these studies, the subjects had to have been postmenopausal, which was confirmed by FHS and estradiol measurements. Because of this and other inclusion/exclusion criteria the subjects in these 5 studies were older and generally healthier (free of concomitant medications) than the pivotal clinical study 366.

Table 14

Baseline Demographics of Pharmacokinetic Studies

Variable	Study #				
	CN054	**BN038**	**930125**	**BN037**	**941817**
Number of subjects	12	36	18	36	24
Age (years)					
Mean	54.3	55.9	53.1	55.2	54.9
Range	49 - 58	49 – 64	43 - 63	49 – 64	43 – 64
Weight (kg)					
Mean	66.4	63.4	64.7	62.6	63.5
SD	6.2	7.7	5.2	6.6	6.1

Study Events

There were not any serious adverse events reported in any of the 5 pharmacokinetic studies. In general, the treatments were similarly well-tolerated. Most of the subjects in these studies did not report any adverse events. In the fasting studies, the majority of the reported events were headaches whereas in the effect-of-food studies, loose stools , headache and abdominal (stomach) cramps were most common, presumably due to the high-fat content of the breakfast.

In Table 15 (fasting studies) and Table 16 (effect-of-food studies) we present a summary of the number and frequency of occurrence of adverse events that were judged by the principal investigator to be possibly, probably or definitely related to the treatment. The events are reported only for those subjects in the Cenestin™ treatment periods.

Continued on next page

Ancillary Studies, Continued

Table 15

Occurrence of Adverse Events in the Fasting Pharmacokinetic Studies

Adverse Event	# Subjects	# Occurrences
Headache	17	34
Hot Flushes	6	9
Nausea	4	5
Tiredness	2	2
Spotting	2	2
Vaginal Secretion	1	1
Sleep Disorder	1	1
Vomiting	1	1
Increase in weight	1	1
Swollen Fingers	1	1
Bleeding like menses	1	1
Retching	1	1
Pressure in head	1	1

Table 16

Occurrence of Adverse Events in the Effect-of-Food Pharmacokinetic Studies

Adverse Event	# Subjects	# Occurrences
Loose Stools	3	12
Headache	4	4
Abdominal cramps	3	3
Nausea	2	2
Dizziness	2	2
Constipation	1	1
Rash on upper body	1	1
Redness on upper body	1	1
Itchiness on upper ankle	1	1
Redness on ankle	1	1
Red spots on abdomen, arm, back, chest and legs	1	1
Sensation of fullness	1	1
Problems digesting all meals	1	1

Conclusion

Pivotal Clinical Study

In the pivotal clinical study the incidence of most estrogen-related side effects was modest but greater in the active treatment group than in the placebo group. Of the known estrogen-related side effects, breast pain was reported in 29% of the active group and 15% in the placebo group. Breakthrough bleeding (metrorrhagia) occurred in 14% of the active treatment group and 6% in the placebo group. Fluid retention (peripheral edema) was reported in 10% of the active treatment group while 13% of the placebo group reported it. Overall, of the 120 patients who enrolled in the study, 111 (93%) reported some form of untoward symptom during the course of the study.

The active treatment group (94%) did not have a higher overall incidence of side effects than the placebo group (90%). Of the 11 patients (5%) who did not complete the study, six (6) patients were dropped from the study for non-serious adverse events(s), three (3) for compliance reasons and two (2) dropped for personal reasons. Of the 6 discontinued patients that reported non-serious adverse event(s), half (50%) were in the synthetic conjugated estrogens treatment group and half (50%) were in the placebo group. No patient dropped from the study because they were unable to control their vasomotor or menopausal symptoms.

Pharmacokinetic Studies

Adverse events reported by subjects in the Cenestin™ treatment groups were generally associated with either known estrogen-related side effects or the stress of the study procedures (i.e., confinement, frequent and often painful blood draws, adherence to rigid schedule and, for the effect-of-food studies, poor acceptance of the high fat breakfast).

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