

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

GASTROINTESTINAL ADVISORY COMMITTEE MEETING, JUNE 26, 2000

PRELIMINARY MEDICAL/STATISTICAL REVIEW

This document addresses the clinical and statistical issues for the application for Zelmac (tegaserod tablets), NDA 21-200. The document does not present the reviewers' final recommendations and should not be viewed as the final review. The document is divided into four sections: background information, comments on study design and analyses, safety, and conclusions.

1.0 BACKGROUND

1.1 Study Description and Sponsor Efficacy Results

This application for Zelmac (tegaserod) was submitted for the indication of the treatment of irritable bowel syndrome in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms (C-IBS).

Three Phase 3 studies were submitted in the application: B301, B307, and B351. The designs and patient populations in the three studies were similar. Each study was a 16-week (a 4-week baseline period and a 12-week treatment period), double-blind, placebo-controlled, parallel group, double-dummy, multicenter, and multinational study in male and female outpatients aged 18 years or older with constipation-predominant irritable bowel syndrome (C-IBS). Each study consisted of a 4-week baseline period (with no placebo) and a 12-week double-blind treatment period. Patients took their treatment tablets in a double-dummy fashion, with water, within 30 minutes prior to meals in the morning and evening. Patient clinical visits were monthly. The target enrollment for entry into the randomized double-blind phase of each study was 693 intent to treat patients in approximately 50 centers.

Studies B351 and B301 had identical study designs: following a 4 week baseline period, eligible patients were randomized, in equal allocation (231 patients per treatment group), to receive either placebo, 4 mg/d or 12 mg/d of tegaserod. In Study B307, following a 4 week baseline period, eligible patients were randomized, in equal allocation (231 patients per treatment group), to receive either a fixed dose of 4 mg of tegaserod, a dose-titration regimen or placebo. The patients randomized to dose-titration received 4 mg of tegaserod and underwent dose titration at week 4 to 12 mg if the response on the SGA of relief was complete or considerable relief <50% of the time. Patients in the 4 mg and placebo groups underwent a mock dose titration at week 4.

Each study's objective was to determine the efficacy of two dose levels of tegaserod by comparison to placebo. Efficacy was defined as the relief of constipation, pain, and discomfort. Efficacy was assessed based on the following two primary efficacy measures that were evaluated by the patient on a weekly basis:

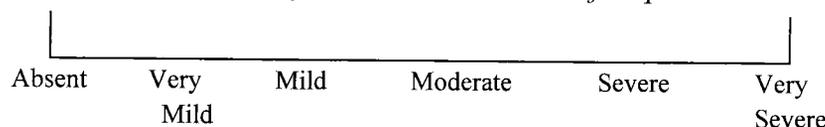
- Subject Global Assessment of Relief - Patients responded to the following question:

"Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week?"

The choices were: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. The definition of responder at endpoint for this variable was defined as follows:

- At least 50% of the SGAs at endpoint with complete or considerable relief
 - Number of days with laxative* use during treatment period ≤ 5 and no laxative* use during the last 28 days of treatment (* with the exception of bulk-forming laxatives)
 - Duration of exposure to study medication ≥ 28 days
 - At least one post-baseline SGA of relief
- Subject Global Assessment of abdominal discomfort/pain (a 100 mm VAS with verbal descriptors for abdominal discomfort/pain) - Patients placed a vertical mark on the line in response to the following question:

"How much of a problem was your abdominal discomfort/pain over the last week?"



The definition of responder at endpoint for this variable was defined as follows:

- a ≥ 20 mm and $\geq 40\%$ reduction in mean VAS at endpoint compared to the baseline
- Number of days with laxative* use during treatment period ≤ 5 and no laxative* use during the last 28 days of treatment (* with the exception of bulk-forming laxatives)
- Duration of exposure to study medication ≥ 28 days
- At least one post-baseline SGA of relief

All three studies began at about the same time but study B351 was completed before the other two. Study B351 was unblinded and the data were analyzed according to protocol. The results for the two primary efficacy variables of SGA of relief and SGA of abdominal pain/discomfort were not statistically significant. This prompted the sponsor to redefine the responders for the SGA of relief variable and drop the co-primary variable of SGA of abdominal discomfort/pain to a secondary variable after post-hoc analyses of the data for study B351. These changes were submitted as protocol amendments to be applied to the remaining two studies, B301 and B307, which were still ongoing. The new definition of a responder for SGA of relief is as follows:

- At least 50% of the SGAs at endpoint with complete or considerable relief **OR**
All of the SGAs at endpoint with at least somewhat relief (i.e. complete, considerable or somewhat)
- Number of days with laxative* use during treatment period ≤ 5 and no laxative* use during the last 28 days of treatment (* with the exception of bulk-forming laxatives)
- Duration of exposure to study medication ≥ 28 days
- At least one post-baseline SGA of relief

A detailed description of these amendments and the sponsor's rationale for the changes are presented in section 1.2. Because of the hypothesis generating nature of the post-hoc data analysis of study B351, the Division deemed that study B351 was no longer pivotal.

Patient Demographics

Table 1.1 presents a summary of the patient demographics for the ITT population. The number of patients randomized to studies B301, B307, and B351 are 881, 841, and 799, respectively. In all three studies there were more females (83% to 87%) than males (13% to 17%), the majority of

patients were Caucasian (88% to 98%), the majority of the patients were less than 65 years old (89% to 93%), and the mean duration of C-IBS symptoms was 13.2 to 14.6 years.

Table 1.1
Demographics and Baseline Characteristics for ITT Population by Study

	B301 (N=881)	B307 (N=841)	B351 (N=799)
Gender – N (%)			
Male	150 (17.0)	138 (16.4)	102 (12.8)
Female	731 (83.0)	703 (83.6)	697 (87.2)
Race – N (%)			
Caucasian	863 (98.0)	760 (90.4)	702 (87.9)
Black	7 (0.8)	46 (5.5)	68 (8.5)
Other	11 (1.3)	35 (4.2)	29 (3.7)
Age (years) – N (%)			
< 65	787 (89.3)	750 (89.2)	744 (93.1)
≥ 65	94 (10.7)	91 (10.8)	55 (6.9)
Duration of C-IBS symptoms (months)			
Months: Mean (SD)	158.1 (147.6)	166.4 (120.0)	174.6 (120.0)
Years: Mean (SD)	13.2 (12.3)	13.9 (10.0)	14.6 (10.0)

Primary Efficacy: Subject Global Assessment of Relief

The following remarks pertain to the new definition of SGA of relief. The results for the original definition of SGA of relief are presented for completeness to compare the effect of changing the definition of responder. The results for all studies are presented in Table 1.2 and are as follow:

- In study B301, both treatment groups had higher response rates compared with the placebo group. The therapeutic gain was 9% in the 4 mg group and 8% in the 12 mg group, both were statistically significant.
- In study B307, the 4 mg group had a similar response to the placebo group and the 4-12 titration group had a higher response rate compared to the placebo group. The therapeutic gain was 0.8% in the 4 mg group and 6% in the 4-12 mg titration group, neither of which was statistically significant.
- In study B351, both treatment groups had higher response rates compared with the placebo group. The therapeutic gain was 6% in the 4 mg group and 12% in the 12 mg group, of which only the 12 mg group was statistically significant.

Table 1.2
Subject Global Assessment of Relief by Study

	N	Original Definition of SGA of Relief			New Definition of SGA of Relief		
		4 mg (n)	12 mg (n)	Placebo (n)	4 mg	12 mg	Placebo
Study B301							
Response Rate	881	27.8 (299)	26.2 (294)	20.5 (288)	38.8	38.4	30.2
Therapeutic Gain ¹		7.6	5.5		9.1	8.3	
p-value ²		0.028	0.116		0.018	0.033	
Adjusted p-value ³		0.056	0.116		0.033*	0.033*	
Study B307							
Response Rate	841	25.5 (282)	26.5 (275)	28.2 (284)	38.3	42.2	37.0
Therapeutic Gain ¹		-3.0	-1.4		0.8	6.0	
p-value ²		0.422	0.703		0.837	0.142	
Adjusted p-value ³		0.703	0.703		0.837	0.284	
Study B351							
Response Rate	799	29.4 (265)	26.2 (267)	22.1 (267)	38.9	45.7	33.3
Therapeutic Gain ¹		7.5	4.1		6.0	12.4	
p-value ²		0.050	0.266		0.157	0.004	
Adjusted p-value ³		0.200	0.370		0.314	0.016*	

¹ Therapeutic gain is the weighted difference of response rates between the drug group and placebo group, taking into account center effect.

² Nominal p-value based on the Mantel-Haenszel test stratified by center.

³ p-value adjusted using Hochberg's multiple comparison procedure adjusting for two doses in studies B301 and B307, or using Holm's multiple comparison procedure adjusting for two doses and co-primary efficacy variable of SGA of abdominal discomfort/pain in study B351.

* Statistically significant at the 0.05 significance level, using Hochberg's (B301 and B307) or Holm's (B351) multiple comparison procedure.

Secondary Efficacy: Subject Global Assessment of Abdominal Discomfort/Pain

The results for all studies are presented in Table 1.3 and are as follow:

- In study B301, both treatment groups had higher response rates compared with the placebo group. The therapeutic gain was 7% in both the 4 mg group and the 12 mg group.
- In study B307, both treatment groups did not have higher response rates compared to the placebo group. The therapeutic gain was -6% in the 4 mg group and -3% in the 4-12 mg titration group.
- In study B351, both treatment groups had higher response rates compared with the placebo group. The therapeutic gain was 5% in the 4 mg group and 6% in the 12 mg group.

Table 1.3
Subject Global Assessment of Abdominal Discomfort/Pain by Study

Study	N	4 mg (n)	12 mg (n)	Placebo (n)
Study B301				
Response Rate	880	29.8 (299)	29.9 (294)	22.6 (287)
Therapeutic Gain ¹		7.0	7.3	
p-value ²		0.055	0.044	
Study B307				
Response Rate	841	25.5 (282)	27.6 (275)	30.6 (284)
Therapeutic Gain ¹		-5.5	-3.1	
p-value ²		0.141	0.411	
Study B351				
Response Rate	799	23.4 (265)	25.1 (267)	18.7 (267)
Therapeutic Gain ¹		4.8	6.4	
p-value ²		0.185	0.075	

¹ Therapeutic gain is the weighted difference of response rates between the drug group and placebo group, taking into account center effect.

² Nominal p-value based on the Mantel-Haenszel test stratified by country.

1.2 Protocol Amendments

In the original protocol, there was one primary efficacy variable, the Subject Global Assessment (SGA) of abdominal discomfort/pain. Three protocol amendments were subsequently submitted. Discussed below are the 2 protocol amendments that pertain to changes in the statistical design.

The first amendment was written prior to the start of all three studies. Its aim was to:

- introduce a second primary efficacy variable, the SGA of relief, and to adjust for the sample size accordingly (Holm's procedure was introduced, leading to an increase in sample size)
- introduced Holm's procedure to adjust for multiplicity
- The target enrollment for entry into the randomized double-blind phase of the study was increased from 591 ITT patients (in approximately 45 centers) to 693 ITT patients (in approximately 50 centers).

The sponsor's rationale for a second primary efficacy variable was based on the idea that both the SGA of relief and the SGA of abdominal discomfort/pain were considered clinically relevant variables in irritable bowel syndrome. That is, the sponsor was not clear which of the two variables was more meaningful in evaluating C-IBS, so either variable was considered important.

The other amendment was written prior to breaking the double-blind treatment code in studies B301 and B307. Its aim was to:

- modify the responder for the SGA of relief original definition of a single criterion of “considerable or complete relief at least 50% of the time during the last 4 weeks on treatment” to also include the criterion “OR somewhat, considerable, or complete relief for all of the last 4 weeks on treatment”
- introduce a modified primary efficacy analysis where SGA of relief became the only primary outcome measure
- eliminate SGA of abdominal discomfort/pain as a primary efficacy variable and keep it as a secondary variable
- introduce additional secondary efficacy variables
- apply Hochberg’s procedure for the multiple comparisons of the two tegaserod treatment groups versus placebo in the primary analysis

The sponsor’s rationale for modifying the primary outcome measure was based on the low responder rates in both the tegaserod groups and the placebo group in study B351, which indicated that the definition of response for both the SGA of relief and the SGA of abdominal discomfort/pain was too stringent and therefore the response definition appeared to lack the sensitivity to detect a significant treatment effect. The Division considered the change in definition of responder acceptable and requested that the study results be presented using both the original SGA of relief and the new SGA of relief. The reason for presenting both results is to see how the redefinition affected the original study results.

The sponsor’s rationale for eliminating the SGA of abdominal discomfort/pain as a primary efficacy variable and retaining it as a secondary efficacy variable is that there are inherent problems with the use of the VAS, including the patient’s potential difficulties in translating her/his experiences to the scale and the difficulty in defining a responder on the VAS.

1.3 Post-Hoc Analyses

The sponsor has presented post-hoc analyses for the primary efficacy variables pooled across all three studies, across studies B301 and B351, and across studies B301 and B307. The sponsor also presented post-hoc analyses using the number of months (0, 1, 2, or 3 months) that a patient was a responder. In this analysis, only the SGA of relief outcome was used without accounting for laxative use. Comments to these analyses are provided in the following section.

2.0 COMMENTS ON STUDY DESIGN AND ANALYSES

The comments pertaining to the study design and efficacy analyses are primarily statistical. The following issues will be discussed in detail: 1) Efficacy analysis by gender, 2) Change of the primary efficacy variables, 3) Pooling of study centers, 4) Pooling of study results, 5) Laxative use, 6) Expansion of study population, 7) Patient enrollment by centers, 8) Investigator participation in multiple studies, 9) Additional issues.

2.1 Efficacy Analyses by Gender

This section presents the reviewer’s analyses of the primary efficacy variable of SGA of relief and secondary efficacy variable of SGA of abdominal discomfort/pain by gender. The sponsor did not present these analyses by study.

Patient Demographics and Baseline Characteristics by Gender

Table 2.1 presents a summary of patient demographics and baseline characteristics for the ITT population by gender. Several differences in demographics and baseline variables were noted between males and females. Study B301 had more Caucasians for both males and females than the other two studies. Males weighed more than females in all studies. The duration of C-IBS among males was longer in study B307 than the other 2 studies, and in females was longer in study B351 than in the other two studies. Males had less number of days without bowel movements and less percent of days with hard/very hard stools than females in all studies. Male had more bowel movements than females in all studies.

Table 2.1
Studies B301, B307, and B351: Demographics and Baseline Characteristics in the ITT Population by Gender

Demographic/Baseline variable	B301		B307		B351	
	Females (n=731)	Males (n=150)	Females (n=700)	Males (n=135)	Females (n=675)	Males (n=100)
Age (yrs)	45 ± 14	49 ± 14	44 ± 13	49 ± 14	42 ± 12	48 ± 13
Age ≥ 65 years	10%	16%	10%	16%	6%	14%
Race: Caucasian	98%	97%	90%	91%	87%	91%
Race: Black	1%	0%	6%	4%	9%	5%
Race: Other	1%	3%	4%	4%	4%	4%
Weight (kg)	65 ± 13	79 ± 12	68 ± 15	83 ± 15	69 ± 15	86 ± 17
Duration of C-IBS (months)	165 ± 150	127 ± 130	169 ± 150	151 ± 168	181 ± 161	135 ± 144
Abdominal discomfort/pain VAS score (mm)	61 ± 13	57 ± 12	62 ± 13	58 ± 12	64 ± 13	61 ± 10
Bowel habit VAS score (mm)	61 ± 14	56 ± 12	62 ± 14	58 ± 14	65 ± 14	62 ± 13
No. of days/28 days with significant ¹ discomfort/pain	23 ± 6	24 ± 6	24 ± 6	25 ± 6	24 ± 5	25 ± 6
No. of days/28 days with significant ¹ bloating	23 ± 7	23 ± 7	24 ± 6	23 ± 8	25 ± 5	23 ± 8
No. of days/28 days without bowel movements	13 ± 7	9 ± 8	12 ± 7	9 ± 7	14 ± 7	9 ± 8
No. of bowel movements/28 days	20 ± 14	28 ± 22	24 ± 19	30 ± 24	21 ± 16	32 ± 25
% of days ² with hard/very hard stools	29 ± 29	22 ± 27	30 ± 28	24 ± 25	32 ± 29	28 ± 26

Note: results are expressed as mean ± SD.

¹ Defined as at least mild (daily score ≥ 2 on a 6-point scale).

² Denominator is days with bowel movements.

Primary Efficacy: Subject Global Assessment of Relief

Given that a large number of centers did not recruit the minimum of 15 ITT patient per center (see Table 2.4) and that the randomization list was generated by country, centers were pooled across country and country was used as a stratification variable in the primary and secondary efficacy analyses. Also, the therapeutic gain is based on the weighted average of the responder rate. The weight for country k is proportional to $N\{k1\} * N\{k2\} / (N\{k1\} + N\{k2\})$, where $N\{ki\}$ is the number of patients in the i -th treatment group in country k .

Also, the ITT populations for studies B307 and B351 differ from the sponsor's ITT populations. In study B307, the reviewer's ITT population was of size 835 instead of size 841 because one Canadian center with 6 randomized patients was removed from the ITT population. The center was removed because the sponsor suspended the investigator due to audit findings demonstrating significant departures from GCP (good clinical practice). In study B351, the reviewer's ITT population was of size 775 instead of size 799 because two Canadian centers with 18 and 6 randomized patients were removed from the ITT population. Both Canadian centers in the ITT population were removed from the ITT population because:

- The sponsor suspended one center's investigator because audit findings demonstrated significant departures from GCP.

- The other center had 6 randomized patients, which are not enough to include in the analysis as the contribution from Canada.

The results for study B301 are presented in Table 2.2 and are as follow:

- Female patients in both treatment groups had higher response rates compared with the placebo group. The therapeutic gain was 10% in the 4 mg group and 11% in the 12 mg group.
- Male patients in both treatment groups did not have higher response rates compared with the placebo group. The therapeutic gain was 0.5% in the 4 mg group and -8% in the 12 mg group.

Table 2.2
Study B301: Subject Global Assessment of Relief by Gender

	N	Original Definition of SGA of Relief			New Definition of SGA of Relief		
		4 mg (n)	12 mg (n)	Placebo (n)	4 mg	12 mg	Placebo
Male		150					
Response Rate		34.62 (52)	24.00 (50)	29.17 (48)	44.23	36.00	43.75
Therapeutic Gain ¹		5.45	-5.17		0.48	-7.75	
p-value ²		0.269	0.749		0.433	0.555	
Adjusted p-value ³		0.538	0.749		0.555	0.555	
Female		731					
Response Rate		26.32 (247)	26.64 (244)	18.75 (240)	37.65	38.93	27.50
Therapeutic Gain ¹		7.57	7.89		10.15	11.43	
p-value ²		0.039	0.036		0.013	0.006	
Adjusted p-value ³		0.039*	0.039*		0.013*	0.012*	

¹ Therapeutic gain is the raw difference of response rates between the drug group and the placebo group.

² Nominal p-value based on the Mantel-Haenszel test stratified by country.

³ p-value adjusted using Hochberg's multiple comparison procedure.

* Statistically significant at the 0.05 significance level, using Hochberg's multiple comparison procedure.

The results for study B307 are presented in Table 2.3 and are as follow:

- Female patients in both treatment groups had higher response rates compared with the placebo group. The therapeutic gain was 5% in both the 4 mg group and 4-12 mg titration group.
- Male patients in both treatment groups had slightly higher response rates compared with the placebo group. The therapeutic gain was 0.09% in the 4 mg group and 2% in the 4-12 mg titration group.

Table 2.3
Study B307: Subject Global Assessment of Relief by Gender

	N	Original Definition of SGA of Relief			New Definition of SGA of Relief		
		4 mg (n)	4-12 mg (n)	Placebo (n)	4 mg	4-12 mg	Placebo
Male		135					
Response Rate		15.91 (44)	21.95 (41)	32.00 (50)	34.09	39.02	34.00
Therapeutic Gain ¹		-16.09	-10.05		0.09	5.02	
p-value ²		0.143	0.355		0.859	0.455	
Adjusted p-value ³		0.286	0.355		0.859	0.859	
Female		700					
Response Rate		27.54 (236)	27.59 (232)	27.16 (232)	38.98	42.67	37.50
Therapeutic Gain ¹		0.38	0.43		1.48	5.17	
p-value ²		0.914	0.983		0.928	0.285	
Adjusted p-value ³		0.983	0.983		0.928	0.570	

¹ Therapeutic gain is the raw difference of response rates between the drug group and the placebo group.

² Nominal p-value based on the Mantel-Haenszel test stratified by country.

³p-value adjusted using Hochberg's multiple comparison procedure.

* Statistically significant at the 0.05 significance level, using Hochberg's multiple comparison procedure.

The results for study B351 are presented in Table 2.4 and are as follow:

- Female patients in both treatment groups had higher response rates compared with the placebo group. The therapeutic gain was 9% in the 4 mg group and 15% in the 12 mg group.
- Male patients in both treatment groups did not have higher response rates compared with the placebo group. The therapeutic gain was -2% in both the 4 mg group and 12 mg group.

Table 2.4
Study B351: Subject Global Assessment of Relief by Gender

	N	Original Definition of SGA of Relief			New Definition of SGA of Relief		
		4 mg (n)	12 mg (n)	Placebo (n)	4 mg	12 mg	Placebo
Male		100					
Response Rate		24.32 (37)	19.35 (31)	18.75 (32)	32.43	32.26	34.38
Therapeutic Gain ¹		5.57	0.60		-1.95	-2.12	
p-value ²		0.771	1.00		1.00	1.00	
Adjusted p-value ³		1.00	1.00		1.00	1.00	
Female		675					
Response Rate		30.91 (220)	27.19 (228)	22.03 (227)	40.91	46.93	32.16
Therapeutic Gain ¹		8.88	5.16		8.75	14.77	
p-value ²		0.041	0.231		0.062	0.002	
Adjusted p-value ³		0.082	0.231		0.062	0.004*	

Note: Only United States centers were in the ITT population.

¹ Therapeutic gain is the raw difference of response rates between the drug group and the placebo group.

² Nominal p-value based on Fisher's Exact test.

³ p-value adjusted using Hochberg's multiple comparison procedure.

* Statistically significant at the 0.05 significance level, using Hochberg's multiple comparison procedure.

Tegaserod is effective in female patient but no evidence of efficacy is demonstrated for males in these studies. The results for male and female patients may indicate a difference in the pathophysiology of C-IBS between genders. Another explanation for the lack of evidence for efficacy is that there is not sufficient number of male patients in these studies. The overall positive treatment effect seen in the analyses for all patients was driven primarily by the efficacy in female patients.

Secondary Efficacy: Subject Global Assessment of abdominal discomfort/pain

The results for study B301 are presented in Table 2.5 and are as follow:

- Female patients in both treatment groups had higher response rates compared with the placebo group. The therapeutic gain was 9% in the 4 mg group and 10% in the 12 mg group.
- Male patients in both treatment groups did not have higher response rates compared with the placebo group. The therapeutic gain was -2% in the 4 mg group and -5% in the 12 mg group.

Table 2.5
Study B301: Subject Global Assessment of Abdominal Discomfort/Pain

	N	4 mg (n)	12 mg (n)	Placebo (n)
Male				
	150			
Response Rate		26.92 (52)	24.00 (50)	29.17 (48)
Therapeutic Gain ¹		-2.25	-5.17	
p-value ²		0.864	0.985	
Female				
	730			
Response Rate		30.36 (247)	31.15 (244)	21.34 (239)

Therapeutic Gain ¹	9.02	9.81
p-value ²	0.020	0.014

¹ Therapeutic gain is the raw difference of response rates between the drug group and the placebo group.

² Nominal p-value based on the Mantel-Haenszel test stratified by country.

The results for study B307 are presented in Table 2.6 and are as follow:

- Female patients in both treatment groups did not have higher response rates compared with the placebo group. The therapeutic gain was -4% in the 4 mg group and -0.9% in the 4-12 mg titration group.
- Male patients in both treatment groups did not have higher response rates compared with the placebo group. The therapeutic gain was -11% in the 4 mg group and -12% in the 4-12 mg titration group.

Table 2.6
Study B307: Subject Global Assessment of Abdominal Discomfort/Pain

	N	4 mg (n)	4-12 mg (n)	Placebo (n)
Male				
	135			
Response Rate		25.00 (44)	21.95 (41)	34.00 (50)
Therapeutic Gain ¹		-11.00	-12.05	
p-value ²		0.606	0.451	
Female				
	700			
Response Rate		25.85 (236)	28.88 (232)	29.74 (232)
Therapeutic Gain ¹		-3.89	-0.86	
p-value ²		0.273	0.808	

¹ Therapeutic gain is the raw difference of response rates between the drug group and the placebo group.

² Nominal p-value based on the Mantel-Haenszel test stratified by country.

The results for study B351 are presented in Table 2.7 and are as follow:

- Female patients in both treatment groups had higher response rates compared with the placebo group. The therapeutic gain was 5% in the 4 mg group and 7% in the 12 mg group.
- Male patients in the 4 mg group had a higher response rate compared with the placebo group and those in the 12 mg group had a lower response rate compared with the placebo group. The therapeutic gain was 8% in the 4 mg group and -6% in the 12 mg group.

Table 2.7
Study B351: Subject Global Assessment of Abdominal Discomfort/Pain

	N	4 mg (n)	12 mg (n)	Placebo (n)
Male				
	100			
Response Rate		29.73 (37)	16.13 (31)	21.88 (32)
Therapeutic Gain ¹		7.85	-5.75	
p-value*		0.585	0.750	
Female				
	675			
Response Rate		23.18 (220)	25.44 (228)	18.50 (227)
Therapeutic Gain ¹		4.68	6.94	
p-value ²		0.245	0.089	

Note: Only United States centers were in the ITT population.

¹ Therapeutic gain is the raw difference of response rates between the drug group and the placebo group.

² Nominal p-value based on Fisher's Exact test.

2.2 Change of the Primary Efficacy Variables

The sponsor's scientific rationale for changing the co-primary efficacy variable of SGA of abdominal discomfort/pain to a secondary efficacy variable in protocol amendments for studies B301 and B307 is not clear since abdominal discomfort/pain is an important component of C-IBS. The following are three reasons found by the reviewer for the change:

1. The sponsor stated that given both the patient's potential difficulties in translating her/his experiences to the visual analog scale (VAS) and the difficulty in defining a responder, the SGA of abdominal discomfort/pain will be eliminated as a primary efficacy variable and instead be retained as a secondary efficacy variable. Also, in study B351, the two primary efficacy variables (SGA of relief and SGA of abdominal discomfort/pain) had been highly correlated.
2. The sponsor stated that the rationale for reclassifying the co-primary efficacy variable of SGA of abdominal discomfort/pain to a secondary efficacy variable was based on the fact that the VAS measurement was no longer the norm in assessing pain or other outcomes.
3. The sponsor stated that in study B351 the results for SGA of abdominal discomfort/pain were not statistically significant.

2.3 Pooling of Centers

The sponsor developed an algorithm for pooling centers. In this algorithm, centers within a country were pooled to ensure that the pooling criteria (treatment row totals ≥ 2 and response column totals ≥ 1) were fulfilled for both primary variables in all three of the following data sets: ITT population at endpoint, Per Protocol population at endpoint, and ITT population who completed the study. Specifically:

- 3*2 tables were created for each center, with the three treatment groups as row headers and the response status for SGA of relief at endpoint (yes/no) as column headers.
- Centers were sorted by country, center size, and center number in ascending order. Centers with a treatment row total < 2 or a response column total < 1 were placed, by center size and center number, at the top of the respective country category.
- Centers were pooled sequentially by the sorting order in the same country category until fulfilling the pooling criteria.
- The response column criterion had to be fulfilled for each of the two pairwise treatment comparisons, i.e. for the tegaserod 4 mg and placebo, and for the tegaserod 12 mg and placebo comparisons.

The sets of centers after pooling were used as strata in the Mantel-Haenszel analysis of the primary efficacy variable.

This algorithm for pooling centers is not appropriate because it was based on the number of responders and non-responders for each primary efficacy variable after the blind was broken. Using the response column totals as a criterion for pooling after the blind is broken could potentially bias the results of the analyses. A preferable algorithm is one that pools centers within a country based on the total number of patients in the ITT population at that center until a minimum number of patients is achieved.

Given that a large number of centers did not recruit the minimum of 15 ITT patient per center (see item 6. below) and that the randomization list was generated by country, a better algorithm is to pool all centers within a country. The analyses would then be stratified by country.

2.4 Pooling of Study Results

The sponsor has presented the results pooled across studies B301, B307, and B351 are not appropriate. The following three pooled populations were analyzed at endpoint and at month 1:

B351/B301, B351/B301/B307, and B301/B307. Pooling these studies is not appropriate because of the following reasons:

- a. The pooled analyses were not pre-specified in the protocol. The pooled analyses are post-hoc and subject to bias and non-interpretability of any p-values because the decision to pool was data driven.
- b. Assuming pooled analysis was acceptable, this would constitute a single trial necessitating a second trial to provide replication of the pooled study results.
- c. The statistical significance of post-hoc, pooled results is problematic. The p-value from such an analysis is not interpretable because the analysis is data driven and potentially biased. A smaller p-value would be achieved because of the larger sample size (an issue of power).
- d. The sponsor's decision to pool was based on the non-significant results of study B307. Pooling was used to resolve the lack of statistical significance in study B307. Consequently, with pooling, study B307 appears acceptable in the light of a positive overview.
- e. The results of study B351 led the sponsor to change the protocol-specified definition of responder and to make one of the protocol-specified co-primary efficacy variables a secondary efficacy variable for the remaining two pivotal studies. The change was made because the results were not statistically significant in study B351. These changes were then applied to study B351 and gave post-hoc statistically significant results for the 12 mg group. The division deemed that study B351 is not pivotal. Thus, pooling study B351 with the other two pivotal studies is not appropriate since the post-hoc results bias the pooled results in favor of the active treatment.
- f. The three studies are not homogeneous with respect to the following demographic and study characteristics: 1) ethnic composition; 2) the percentage of primary, secondary, and tertiary participating centers; and 3) the baseline use of laxative.

1) The following ethnic composition is found in the three studies: study B301 included European, U.S., South African, Turkish patients; study B307 had European patient only; and study B351 had U.S. and Canadian patients.

2) The percentage of primary, secondary, and tertiary care centers for the three studies are presented in Table 2.8. There was a higher percentage of participating secondary centers in study B301, whereas studies B307 and B351 had a higher percentage of primary care centers.

Table 2.8
Number of Patients at Primary, Secondary, and Tertiary Care Centers

Study	Primary Care n (%)	Secondary Care n (%)	Tertiary Care n (%)
B301 (N=881)	505 (57.3)	309 (35.1)	67 (7.6)
B307 (N=835)	621 (74.4)	174 (20.8)	40 (4.8)
B351 (N=775)	602 (77.7)	111 (14.3)	62 (8.0)

3) The baseline use of laxative is different across studies for each treatment group. Table 2.9 presents the number of patients who took laxatives and/or cathartics during the baseline period of the study. Within the 4 mg group, the percentage of patients (20.2%) in study B307 who took laxatives and/or cathartics was less than in studies B301 and B351 (30.4% and 27.9%). Within the 12 mg group, the percentage of patients (26.2%) in study B351 who took laxatives and/or cathartics was less than in study B301 (30.3%). Within the placebo group, the percentage of patients (24.3%) in study B307 who took laxatives and/or cathartics was less than in studies B301 and B351 (28.8% and 29.2%).

Table 2.9
Number of Patients who Took Laxatives and/or Cathartics during the Baseline Study Period

		n (%)
B301	4 mg (N=299)	91 (30.4)
	12 mg (N=294)	89 (30.3)
	Placebo (N=288)	83 (28.8)
B307	4 mg (N=282)	57 (20.2)
	4-12 mg (N=275)	72 (26.2)
	Placebo (N=284)	69 (24.3)
B351	4 mg (N=265)	74 (27.9)
	12 mg (N=267)	70 (26.2)
	Placebo (N=267)	78 (29.2)

- g. The primary endpoints for all three studies are not the same. Study B351 had two primary efficacy variables, SGA of relief and SGA for discomfort/pain and studies B301 and B307 had one primary efficacy variable, SGA of relief. The pain endpoint was dropped to a secondary endpoint in studies B301 and B307 through a protocol amendment after the sponsor reviewed the results of study B351 (see 2. above).
- h. The study design of study B307 is different from the other two studies. In studies B301 and B351, patients were randomized into one of the following three fixed dose groups: 4 mg, 12 mg, and placebo. In study B307, patients were randomized into one of the following three dose regimen groups: 4 mg fixed dose, 4 to 12 mg titration dose, placebo. The fixed 12 mg group and the 4 to 12 mg titration group cannot be pooled into one group since not all patients in the 4 to 12 mg titration group were at a constant dose.
- i. Study B307 tests a fixed dose regimen and a dose-titrating regimen while studies B301 and B307 test two fixed doses.
- j. Study B307 needs to be analyzed using the original definition of SGA of relief responder because the original definition was used to determine if the patient was to be up titrated after 4 weeks of treatment. In study B307, patients randomized to dose-titration received tegaserod 4 mg and underwent dose titration at week 4 to 12 mg if their response on the SGA of relief was complete or considerable relief less than 50% of the time during the 4 week period, that is, a non-responder. Thus, this study can only be analyzed with the original definition of responder since the category "at least somewhat relief for all 4 weeks," as used in the new definition of responder, was not incorporated in the rule for (dose-titration) defining a non-responder for assignment to up titration from 4 mg to 12 mg after 4 weeks of treatment.
- k. The 4-12 mg dose titration group in Study B307 cannot be combined with the 4 mg group for the month 1 pooled analyses and then with the 12 mg group for the at endpoint pooled analyses. The sponsor stated that at endpoint, the titration group in study B307 was pooled together with 12 mg fixed dose since 65% of the patients in the titration group were titrated to 12 mg, and most of titrated patients were treated with 12 mg for 2 months. At Month 1, the titration group (4-12 mg) in study B307 was pooled together with 4 mg fixed dose since all patients in the titration group were treated with 4 mg in the first month of the treatment.
- l. The sample size for each of the three studies is not small (see item 5. below), like what can be seen with a rare disease, so pooling is not necessary. There is sufficient sample size in each study to give an adequate evaluation of the treatment effect on a per study basis.
- m. The studies are not independent because the same U.S. principal investigators participated in two of the three studies (see item 7. below).
- n. Pooling these three studies, which have varying results, leads to an overall result that does not provide a useful guide to physicians.

2.5 Laxative Use

All per protocol and post-hoc analyses need to take into account laxative use. Laxative use is a confounding variable in the response of a patient to the efficacy variable of SGA of relief and any other efficacy variable. It is difficult to totally ignore the effects of laxative use in any study that evaluates patients with constipation. Per protocol, laxative use was permitted for purposes of rescue therapy. A patient could use laxative up to 4 times in the first two months of treatment and still be considered a responder. Also, not adjusting for laxative use inflates the responder rates in all treatment groups.

Additionally, information about the use of bulking agents was not adequately collected. Per protocol, patients taking chronic stable doses of bulking agent could continue to do so but there was no data collected about the amount of bulking agent used or the frequency of use by the patient while on treatment. This unquantified use of bulking agents throughout the studies may add an unknown confounding variable.

2.6 Expansion of Study Population

Studies B301 and B307 recruited more patients to the ITT population than was planned for in the protocol. Table 2.10 presents an overview of the sample size for studies B301 and B307. The original protocol, with one primary efficacy variable tested at two dose groups compared to placebo called for a total of 531 patients in the ITT population. An amendment to the protocol, which increased the number of primary efficacy variables to two tested at two dose groups compared to placebo, called for a total of 693 patients in the ITT population. Another protocol amendment, which changed the number of primary efficacy variables to one tested at two dose groups, made no adjustment to the sample size. The final number of patients in the ITT population for studies B301 and B307 were 881 and 835, respectively.

Table 2.10
Sample Size* Overview for Studies B301 and B307

	Study B301 N (n per group)	Study B307 N (n per group)
Original Protocol ITT Population Sample Size	531 (197)	531 (197)
Number of Primary Variables	1	1
First Protocol Amendment ITT Population Sample Size	693 (231)	693 (231)
Number of Primary Variables	2	2
Second Protocol Amendment ITT Population Sample Size	693	693
Number of Primary Variables	1	1
ITT Population Sample Size at End of Study	881	835
Sample Size at Study End Increase from Original Protocol	350	304
% Increase from Original Protocol	69.5%	57.2%
Sample Size at Study End Increase from First Amendment	188	142
% Increase from First Amendment	27.1%	20.5%

* Sample size calculations assumed a placebo responder rate of 0.30, an active treatment effect of 0.45 for both doses (resulting in a 0.15 difference in response rates), 80% power, 0.05 significance level, and adjustment for multiple comparisons (two doses) using either Holm's or Hochberg's procedure for multiple comparisons.

Source: Statistical Reviewer's listing.

The final sample size was over 55% larger than what was planned for in the original protocol, which also had one primary efficacy variable tested at two dose groups compared to placebo. In addition,

the final sample size was over 20% larger than what was planned for in the first amendment, whose protocol had two primary efficacy variables tested at two dose groups compared to placebo. In response to a question from the reviewer about the over recruitment of patients, the sponsor responded that there was no prospective decision to recruit and randomize more than 231 patients per study arm in each of these studies [B301 and B307]. At the end of the enrollment phase in each of these studies, the sponsor allowed patients who had entered the baseline phase of the study [who signed informed consent] to continue on through randomization and complete the study because those patients had undergone diagnostic procedures, including endoscopy. The sponsor felt that patients completing the baseline should be allowed to complete the study. This resulted in an over-enrollment for each study.

The reviewer is not clear why the sponsor did not end enrollment once the target ITT population size for the second protocol amendment was reached. These larger sample sizes result in an increase in the power of the statistical tests for the primary efficacy outcomes.

2.7 Patient Enrollment by Centers

Recruitment of the per protocol minimum number of patients at each study center for the ITT population in studies B301, B307, and B351 was not achieved at all centers. Per protocol, each study center was to recruit a minimum of 15 ITT patients up to a maximum of about 30 ITT patients. Table 2.11 presents a listing of the number of centers that recruited the minimum of 15 ITT patients. The proportion of centers that had at least 15 patients was 22%, 39%, and 51% for studies B301, B307, and B351, respectively. This lack of recruitment of at least 15 ITT patients per center may have resulted from adding more centers to each study. The protocol specified that each study would have approximately 50 centers. Instead, study B301 had 95 centers and study B307 had 66 centers in the ITT population.

Table 2.11
Number of Centers that Recruited a Minimum of 15 ITT Patients, by Country

Country	Study B301		Study B307		Study B351	
	Number of Centers	Number of Centers that had at least 15 patients	Number of Centers	Number of Centers that had at least 15 patients	Number of Centers	Number of Centers that had at least 15 patients
Austria	3	3	-	-	-	-
Belgium	-	-	3	0	-	-
Canada	-	-	3	0	2	1
Finland	4	1	-	-	-	-
France	-	-	8	3	-	-
Germany	16	7	5	1	-	-
Italy	7	2	-	-	-	-
Netherlands	12	1	-	-	-	-
Portugal	2	0	-	-	-	-
South Africa	6	0	-	-	-	-
Spain	1	0	1	1	-	-
Switzerland	9	2	-	-	-	-
Turkey	6	1	-	-	-	-
United Kingdom	18	4	10	2	-	-
United States	11	0	37	19	47	24
Total	95	21 (22.1%)	67	26 (38.8%)	49	25 (51.0%)

Source: Statistical Reviewer's listing.

2.8 Investigators Participation in Multiple Studies

Participation in more than one Phase 3 study by the same principal investigator does not meet the assumption of independent studies. Of the 11 U.S. centers in study B301, 8 came from the U.S. centers in study B351 and three from the U.S. centers in study B307. Of the 41 U.S. centers in study B307, 9 came from the U.S. centers in study B351. Study B351 was completed before both studies B301 and B307 were completed. It was after study B351 was completed that the principal investigators participated in the other studies. The same is true for those principal investigators in study B307 who participated in study B301.

2.9 Additional Issues

Responding to a question from the reviewer about when the randomization lists were generated, the sponsor stated that they were generated on June 24, 1997. An inconsistency arises in the randomization lists for study B301 that show the following date information:

- The randomization lists for the Netherlands, the United States, and South Africa come from files dated in 1998.
- A second randomization list for the United Kingdom and for Germany come from files dated in 1998.
- All other randomization lists are from files dated in 1997.

This reviewer is not clear why the dates differ. The reviewer has no comment on the other two studies because the randomization lists were not included in the submission.

The sponsor acknowledged in a correspondence that protocol amendments were not prepared for the following items:

- Per protocol, study B301 was a European study. The study report in the application includes the United States and South Africa as additional countries.
- Per protocol, studies B301 and B307 were each to have approximately 50 centers total in the ITT population. The study reports in the application show that study B301 had 95 centers and study B307 had 66 centers in the ITT population.

Ethnic differences may have to be considered in view of the difference in symptoms and natural history of C-IBS among ethnic groups. The following ethnic composition is found in the three studies: study B301 included European, U.S., South African, Turkish patients; study B307 had European patient only; and study B351 had U.S. and Canadian patients. Also, the percentage of blacks in studies B301, B307, and B351 was 1%, 6%, and 9%, respectively. The applicability of the results to the U.S. population will have to take into consideration the fact that the representation of the black population in the U.S. was not adequate.

The percentage of males in each study ranged from 13% to 17%. This small number of male patients may not be adequate to evaluate efficacy in this population. Also, by gender analyses suggest that males may respond differently to treatment.

3.0 SAFETY

3.1 Clinical Safety Issues

A total of 1679 patients received Tegaserod at the dose ranging from 4 mg/d to 12 mg/d in Phase 3 studies of 12-week duration. Approximately 70% of patients received treatment for 85 days or longer.

Adverse events (AEs) were reported in 6.8% of patients receiving Tegaserod compared to 5.1% of patients receiving placebo. The most frequent AE was headache, which occurred in about 20% of patients in all treatment groups, including placebo. Other AEs included GI events, backpain, influenza-like symptoms, UTI, dizziness. Except for diarrhea, there was no difference in the incidence of AEs between the treated and placebo groups or relationship to Tegaserod dose. Diarrhea was reported by 11.7% and 5.4% of Tegaserod-treated and placebo patients respectively. Diarrhea occurred during the first week of therapy, and in about half of cases during the first day of therapy. Overall, 2.1% of patients discontinued treatment because of diarrhea.

A total of 8.4% of Tegaserod-treated patients discontinued treatment primarily because of GI adverse events compared to 6.3 patients in the placebo group.

A total of 1.9% of patients experienced serious adverse events (SAEs) in Phase 2 and 3 clinical trials, the incidence of SAEs increased to 4.1% in the long-term study. Four SAEs were reported by the sponsor as possibly or probably related to study drug: abdominal pain (2), gastritis (1), supraventricular tachycardia (1), hypoglycemia (1).

Dizziness occurred in 5-6% of patients with equal frequency between treated and placebo patients. The incidence of postural hypotension was also similar, but syncope occurred more frequently in patients treated with Tegaserod (0.5%) than on the placebo group (0.1%).

A total of 567 patients (>90% Caucasian females) have been evaluated in a long-term safety study, of these patients, more than 150 have received Tegaserod for 365 days and more than 290 have received Tegaserod for more than 290 days. Discontinuation has occurred in 12% of patients due to lack of efficacy and in 11% of patients because of GI adverse events, mainly diarrhea, or headache.

The effects of Tegaserod and of its main metabolite on cardiac repolarization were assessed in three in vitro studies and in one in vivo study of ECG parameters in dogs. No effect on QT prolongation was observed at therapeutic plasma concentrations. No effects of Tegaserod were observed in the Phase 3 and in the long-term clinical trials on ECG. Thus far, there appears to be no difference in ECG parameters between Tegaserod-treated and placebo patients.

Nine cases of ovarian cyst (8 Tegaserod, one placebo patient) were reported in the Integrated Summary of Safety (ISS). Five cases occurring in Tegaserod-treated patients required surgery. Case Report Forms are available for the 5 patients undergoing surgery (Appendix 1). Only limited information is available on the 3 patients who did not undergo surgery. Two patients, one in the Tegaserod and 1 in the placebo group were diagnosed as having Polycystic Ovarian Syndrome not requiring surgery. No additional information is available on these patients.

The estimated frequency of ovarian cysts in tegaserod users is 0.3% per 100,000 women-years (95% CI= 0; 4057) and 0.1% of placebo users per 100,000 women-years (95% CI=0; 4057). Although the incidence of ovarian cysts does not seem to be different from that in the general population, the cases reported for the Tegaserod patients resulted in hospitalization and surgical intervention. Further evaluation of the relevance of these findings is required.

3.2 Preclinical Safety Issues

In a two-year oral (dietary) carcinogenicity study in mice, (CD-1), treatment with SDZ HTF 919 at 600 mg/kg/day produced mucosal hyperplasia (in 13.3% males and 11.7% females) and adenocarcinoma (in 10% males and 3.3% females) of small intestines. Treatment with lower doses of 200 and 60 mg/kg/day did not produce such effects. Adenocarcinoma of small intestine is a rare tumor for mice and as well as humans. The implications of the findings in the context of human safety are unclear at present.

Treatment of female rats (HanIbm Wistar) with SDZ HTF 919 at 20, 80 and 180 mg/kg/day (in diet) for 110 weeks produced dose-related increase in the incidence of "Ovarian" cysts (12, 14 and 20%, respectively) when compared to incidence in controls (0 to 4%). In rats, ovarian follicular cysts can be produced by exposure to constant light, or androgens during neonatal period, or by induced hypothyroidism. The sponsor has conducted histopathology reevaluation of the ovarian material from the rat studies. The relevance of the findings in rats and the implications in the context of the incidences of ovarian cysts noted in women treated with Tegaserod are unclear.

4.0 CONCLUSIONS

Three clinical studies were submitted to the application for Tegaserod, which is indicated for the treatment of patients with constipation predominate irritable bowel syndrome. Two of the three studies were pivotal and one was supportive. Efficacy was demonstrated for only one of the two pivotal studies for both the 4 mg and 12 mg doses. The supportive study demonstrated efficacy for the 12 mg dose only.

Given that all three clinical studies included 15% males on average, a by gender analysis demonstrated efficacy only in female patients. Analyses of the efficacy results for the male population as a separate group failed to show statistical significance. Additional studies with larger male population are required to determine whether the compound is also efficacious in males.

In addition to gender differences, ethnic and racial patient representation need further assessment. The Phase 3 clinical trials included patients from countries such as Turkey and South Africa where the symptoms and natural history of IBS are not well standardized. The percentage of blacks in the clinical trials ranged from 1% to 9%, not representative of the percentage of blacks in the U.S.

The potential confounding effect of laxative use remains to be determined given the fact that the studies evaluated the effectiveness of Tegaserod in constipation predominant IBS.

Tegaserod exhibited a favorable safety profile with no evidence of systemic effects other than gastrointestinal. Diarrhea appeared to be self-limited and required discontinuation in 2.1% of patients.



Study/Patent identity B209/011/0039

Sex, age, race: female, 50yr, Caucasian
Past history: menometrorrhagia, ovarian cyst

Summary case history: **bilateral ovarian endometriosis, serous cystadenofibroma of L-ovary**

The patient began treatment in this 12 month open-label study on 18 Sep 1997.

She underwent surgery for an ovarian cyst on day 334 of the study. She subsequently developed peritonitis as a post-operative complication which was successively treated medically. The patient did not recommence treatment with tegaserod. (Previously, on day 13 of the study, she had been hospitalized for 4 days for acute appendicitis which resolved satisfactorily with treatment.)

The investigator indicated that it had been known that the patient had a L-ovarian cyst since at least ten years and which was symptomless with the surgery not being due to any worsening of the condition.

The patient's gynecologist who referred the patient for surgery has indicated that the patient had a history of cyst three years before the study (1994) but that the 'cyst in question' was found in April 98. However, he has reported the pathology as bilateral ovarian endometriosis and a benign serous adenofibroma of the left ovary.

Discharge notes & pathology report from the hospital in which surgery was performed were requested but have proved impossible to obtain.

Attachments: Original serious adverse report from investigator; subsequent statement from investigator concerning pre-existing nature of condition; note from treating gynecologist.

Accessory information (from case record form):

Study medication administration

Medication	Dosage (mg/d)	Dates
tegaserod	4	18 - 30 Sep 97
	4	20 Nov - 18 Dec 97
	12	18 Dec 97 - 17 Aug 98

Prior/Comedication

Medication (route)	ATC class	Dates
microlax (rectal)	enema	28Sep97
ciprofloxacin (iv/oral)	fluoroquinolone	17-26Aug98
metronidazole (oral)	imidazole derivative	30Sep-4Oct97
metronidazole (iv)		17-26Aug98
panadeine co (oral)	natural opium alkaloid	17-26Aug98
ketogin (im)	opoid +anti-spasmodic	17-20Aug98
naproxen (oral)	propionic acid derivative	26Nov97-6Feb98
albyl-enterosolubile (oral)	salicylic acid derivative	3-6Feb98
doxycycline hyclate (oral)	tetracycline	30Sep-4Oct97

All reported adverse events

Event	severity	Start date	Relationship*
appendicitis	severe	30Sep-4Oct97	unlikely
myalgia	moderate	26Nov-18Dec97	unlikely

Event	severity	Start date	Relationship*
		3-6Feb98	unlikely
ovarian cyst	moderate	17Aug98	unrelated
peritonitis	severe	17-26Aug98	unrelated

* relationship with study medication as assessed by investigator

SANDOZ PHARMA

Page:

SDZ HTF 919

Study Code: HTFB 209-E-00

ID M 37

Subject's initials

SAE

SERIOUS ADVERSE EVENT REPORT

In addition, please complete the 'ADVERSE EVENTS' form

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STUDY MEDICATION

Daily dose 6mg x 2

Start date of medication 18/09/94

Route of administration PO

Time elapsed between last drug administration and onset of event 12 hours

Dose reduction because of event No Not Applicable Yes - Date

Discontinuation because of event No Yes - Date 17/08/98

Code broken No Not Applicable Yes - Name of drug received

CONCOMITANT MEDICATION

Drug name	Indication	Daily dose at time of event	Route of administration	Start date	End date
Flagyl	Pancreatitis	7500mg	IV	17.0898	26.0898
Ciproxin	- r -	4mg	IV	17.0898	23.0898
Ciproxin	- r -	1000mg	PO	23.0898	26.0898
Ketogan	- r -	1ml	IM	17.0898	20.0898
Paralgin forte	- r -	PRN	PO	17.0898	26.0898

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Page 2

ASSESSMENT OF CAUSALITY

Event causality Study indication Concomitant therapy Other, specify Coexistent medical condition Study medication

Relationship to study medication Not related Unlikely Possibly Probably Definitely

Justification of assessment given in Assessment of Causality (e.g. study indication, consistent medical condition, concurrent therapy, study medication, other)
There is NO known causality or reason.
Additional remarks

Institution
Investigator's name (please print) Frank S. ...
Investigator's signature [Signature]
DR. KHEL ERIC LANGRISH
14770 DALHOUSIE ST. # 1111
DASO 1

SAE2-IND-NEW-SAVE / 29 Oct 95

Fredrik Hancke

MEDISIN

Fødselshjelp og kvinnesykdommer

SAE

Priv prakt spes. Ol. Kjell Langaker
Hier. Heyerdahlsgt 1
0160 OSLO

Oslo, 16.03.2000

EPIKRISE

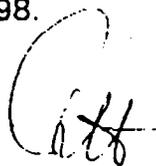
AD

Født: 06/12/1946 41401

Etter pasientens ønske blir følgende opplysninger formidlet:

17/8/98 ble overnevnte operert _____ sykehus pga ovarial tumor.
Histologi viste " endometriose i begge ovarier og serøst cystadenofibrom
(benignt) i ve ovarium. (DNR prep 17172/98)".
Hun hadde forut for dette punktert en cyste 1994 og den aktuelle cyste ble
påvist i april 1998.

Vennlig hilsen



Fredrik Rolf Hancke
Spesialist i kvinnesykdommer og fødselshjelp

Fredrik Hancke
MDNEF
Specialist in obstetrics and women's diseases

Private practising specialist Dr Kjell Langaker
Hier. Heyerdahlsgt. 1
0160 OSLO

Oslo, 16.03.2000

Medical history
Regarding _____ born 06.12.46

According to the patient's wishes the following information is communicated:

17.08.98 was above mentioned operated at _____ hospital due to ovarian tumour.
Histology showed "endometriosis in both ovaries and serous cystadenofibromas
(benign) in left ovary. (DNR prep 17172/98)".
Before this she had punctured a cyst 1994 and the cyst in question was found in April
1998.

Kind regards

Fredrik Rolf Hancke
Specialist in women's diseases and obstetrics

B209/11/89



KJELL ERIK LANGAKER
Lege MDnlf
Spes. indremedisin og lungesykdommer
Allergologi

H. Heyerdahls gt. 1 - 0160 Oslo
Inng. fra Tordenskiolds gt.
Telefon 22 00 81 10 - Telefax 22 00 81 11

NOVARTIS NORGE AS.
BRYNSALLEEN 4
POSTBOKS 237 ØKERN
0510 OSLO

Oslo 1 08.02.00

Pasient :
Adresse :
Poststed:
Diagnose: _____

Født: 06.12.46
Tlf: 67123248

STATEMENT - PATIENT 011 0039/INITIALS

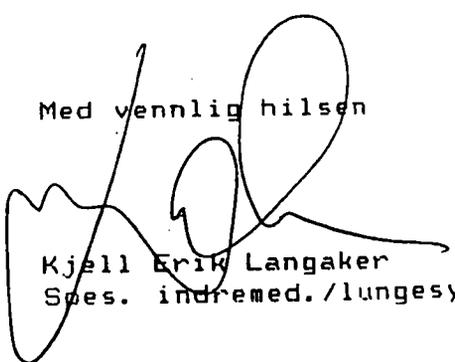
TO WHOM IT MAY CONCERN:

PATIENT 011 0039 / HAD A "WATER" CYST WHEN SHE ENTERED
CLINICAL TRIAL HTFB 209.
IT HAS BEEN PRESENT FOR AT LEAST 10 YEARS BEFORE SHE ENTERED THE
TRIAL. SHE HAD NO SYMPTOMS AND HER CONDITION (THE CYST) DID NOT
GET WORSE DURING THE TRIAL. BY COINCIDENCE SHE RECEIVED A
OPERATION DURING THE STUDY TO REMOVE THE "WATER" CYST ON HER LEFT
OVARIE.

THE HISTOLOGICAL EXAMINATION SHOWED THAT THE CYST WAS BENIGN.

SHE IS IN GOOD HEALTH.

Med vennlig hilsen


Kjell Erik Langaker
Spes. indremed./lungesyk.



Study/Patent identity B209/26/6

Sex, age, race: female, 45yr, Caucasian

Past history: hysterectomy (reason unknown), headaches, seasonal allergies, gastric reflux

Summary case history: bilateral salpingo-oophorectomy for pelvic adhesions

The patient began treatment in this 12 month open-label study on 26Dec 1996. She was hospitalized on 12Sep97 (day 245) after two days of left lower abdominal pain which in his original serious adverse report was attributed by the investigator to an ovarian cyst. The preoperative work-up (hospital report), including CT scan of pelvis & abdomen, US scan of pelvis and barium enema, was inconclusive but considered adhesions to be the most likely diagnosis and this was confirmed in the operative report and discharge summary. The patient underwent a bilateral salpingo-oophorectomy for multiple adhesions of gut and ovary to the L-pelvic wall along with a bladder repair for the coexisting stress urinary incontinence. There is no record of a request for pathology in the hospital file. The investigator considered the episode as unrelated to the study medication and has reevaluated the event, modifying the diagnosis to that of adhesions.

(The patient subsequently recommenced treatment but refused to attend for her final visit)

Attachments: original serious adverse event report from investigator; pre-operative hospital report; operative report; discharge summary; statement from investigator reevaluating event as adhesions.

Accessory information (from case record form):

Study medication administration

Medication	Dosage (mg/d)	Dates	
tegaserod	4	26Dec96 - 23Jan97	
	12	23Jan97 - 10Sep97	(although diary logs missing partially)
	12	18Sep97 - 3Mar98	(final visit due end Dec97. Refusal documented Mar98.)

Prior/Comedication

Medication (route)	ATC class	Dates
Paracetamol (oral)	Anilides	Prior (1985)-cont.
Hyoscyamine sulfate (oral)=	Belladonna alkaloids	Prior (1991)-Dec96
Famotidine (oral)	H2-receptor antagonist	Prior (1991)-cont.
Diltiazem hydrochloride (oral)	Benzothiazepine derivative	Prior (Oct 1996)-cont.
Ketorolac tromethamine (oral)	Acetic acid derivative	15Apr-1Oct97
Premarin with methyltestosterone (oral)	Androgens & estrogens	16Oct97-cont.
Vocodin (oral)	Anilides	28Aug-7Sep97
Alprazolam (oral)	Benzodiazepine derivative	15Sep97-cont.
Doxidan (oral)	Contact laxative	25Apr97-cont.
Phillips laxcaps (oral)	Contact laxative	23Jan97-cont.
Totolin (oral)	Expectorant	24Mar97
Simvastatin (oral)	HMG-CoA reductase inhibitor	10Feb97-cont.
Butorphanol tartrate (nasal)	Morphinan derivative	1-11Sep97
Nitrofurantoin (oral)	Nitrofurantoin derivative	13-21Sep97
Nabumetone (oral)	Other anti-inflammatory/rheumatics	25Jul-8Aug97
Phenazopyridine hydrochloride (oral)	Other urologicals	21-30Sep97
Amoxicillin trihydrate (oral)	Broad spectrum penicillin	4-14Jan97

Medication (route)	ATC class	Dates
Naproxen (oral)	Propionic acid derivative	3-6Jan97
Tetracycline (oral)	tetracyclines	21Sep-1Oct97
Flavoxate hydrochloride	Urinary antispasmodic	20-23Jun97
vitamins	vitamins	16Oct97-cont.

All reported adverse events

Event	severity	Dates	Relationship*
Accidental trauma	moderate	2-6Jan97	unrelated
pain	moderate	12Sep-1Oct97	unrelated
Abdominal pain	severe	27-29Aug97	unrelated
hypercholesterolemia	moderate	23Jan97-cont.	unrelated
tendinitis	moderate	25Jul97-cont.	unrelated
anxiety	moderate	12Sep97-cont.	unrelated
Ovarian cyst	severe	12-15Sep97	unrelated
sinusitis-	moderate	3-14Jan97	unrelated
cystitis	moderate	12Sep-1Oct97	unrelated
dysuria	mild	20-23Jun97	unrelated

* relationship with study medication as assessed by investigator

B 209/26/6

SANDOZ PHARMA

SDZ HTF 919

Study Code: HTFB 209-E-00

ID 26 6
Centre no. Subject no.

SAE

Subject's initials

Date of report 09 16 97
month day year

SERIOUS ADVERSE EVENT REPORT

*See attached Instruction Sheet for information on completion of SAE Form.
In addition, complete the ADVERSE EVENTS FORM

Date of birth 05 17 51
month day year

Weight 133
lb

Height 60
in

Sex Male Female

Race Caucasian Black Asian/Oriental

Pregnant Yes No Not Applicable

Other (specify): _____

Relevant medical history Initial SAE of pain in lower left abdomen, evaluated and diagnosed as ovarian cyst

ADVERSE EVENT specify as reported on AE form:

Clinical description (incl. diagnosis) Surgery performed on 9/12/97 to remove ovaries and performed bladder repair which was assessed as necessary during surgery. All findings were reported as benign.

Reason for reporting
 Requires or prolongs hospitalization Cancer Life-threatening Death
 Persistently disabling or incapacitating Congenital anomaly Overdose
 Other (specify): _____

Start date 09 12 97 Start time _____ End date 09 15 97 End time _____
month day year 24 hr. clock month day year 24 hr. clock

Relevant findings (e.g. ECG, autopsy, lab data, incl. copies of lab sheets) Awaiting reports

Therapeutic measures unknown at this time with exception of surgery

Course and outcome HTFB/209/0/26/6/2/USA
HTFB-209-26-006

COPIES
SEP 17 1997
CSRE

SANDOZ PHARMA

SDZ HTF 919

Study Code: HTFB 209-E-00

ID 26 6
cont. no. subject no.

Subject's initials

SAE

SERIOUS ADVERSE EVENT REPORT

In addition, please complete the 'ADVERSE EVENTS' form

STUDY MEDICATION

Daily dose 6 mg

Route of administration PO

Start date of medication 12 26 1996

Time elapsed between last drug administration and onset of event Approximately 12 hours

Dose reduction because of event No Not Applicable Yes → Date 09 11 1997

Discontinuation because of event No Yes → Date

Code broken No Not Applicable Yes → Name of drug received

CONCOMITANT MEDICATION

Drug name	Indication	Daily dose at time of event	Route of administration	Start date	End date

ASSESSMENT OF CAUSALITY

Event causality Study indication Coexistent medical condition Concomitant therapy Study medication Other, specify

Relationship to study medication Not related Unlikely Possibly Probably Definitely

Justification of assessment given in Assessment of Causality (e.g. study indication, coexistent medical condition, concomitant therapy, study medication, other)

Additional remarks Patient did not take study drug from 9/11/97 until 9/17/97

Institution

Investigator's name (please print) David Mertis, D.O.

Investigator's signature

RECEIVED
SEP 17 1997
CS&E

HTFB/209/0/26/6/2/USA
HTFB-209-26-006

~~6204~~
~~CERTIFIED~~
~~PATIENT 16~~

TO: Pat Regis

COMPANY: _____

FAX NUMBER: _____

Cover sheet + 7 Page(s)

FROM: _____

+++++

NOTES: Pat, according to the operative report there is no mention of any pathology sent out. and no reports were found. Sorry I tried.

FAX NUMBER: _____

PHONE NUMBER: _____
11/7/00
Forwarded all 4 pages of OP Report + 3 pages Discharge Summary to above

B209
CENTER 26
PATIENT 6

I 9/15

Job# 9139/24
TR: _____

DD: 09/15/97
DT: 09/17/97

DISCHARGE SUMMARY

PATIENT: _____
DATE OF ADMISSION: 09/12/97
DATE OF DISCHARGE: 09/15/97

MEDICAL RECORD NO: _____
CASE NO: _____
PHYSICIAN: _____

LABORATORY DATA:
Blood type A, Rh positive, antibody screen negative. Postoperative hemoglobin was 11.0.

- ADMITTING DIAGNOSIS:
1. Pelvic pain.
 2. Stress urinary incontinence.

- DISCHARGE DIAGNOSIS:
1. Pelvic pain.
 2. Stress urinary incontinence.

HISTORY OF PRESENT ILLNESS:
This patient is a 46-year-old white female admitted for exploratory laparotomy, bilateral salpingo-oophorectomy and Marshall-Marchetti-Krantz procedure.

HOSPITAL COURSE:
The patient was taken to surgery on the day of admission where the procedure were performed. The patient was noted to have multiple adhesions of the gut and ovary to the left pelvic side wall, and bilateral salpingo-oophorectomy was performed as well as Marshall-Marchetti-Krantz procedure.

The patient tolerated the procedure well and postoperatively developed some postoperative nausea and anxiety. The patient had urinary retention after discontinuation of her Foley catheter on Saturday morning, and she had to have it replaced, and on Sunday voided well and had problems with nausea. She developed some hallucinations on Darvocet N 100, and the patient was switched off this medication.

DISPOSITION:
She was discharged on the third postoperative day. The patient was given postoperative instructions and was asked to return to the office in two weeks for routine postoperative care.

B209
CENTER 26
PATIENT 6

DISCHARGE SUMMARY
PAGE 2

DISCHARGE MEDICATIONS:
Xanax in the day time, Restoril at bed time and also was given a
prescription for Toradol for pain.

B209

CENTER 26

DD: 09/12/97 PATIENT 6
DT: 09/15/97

Job #: _____
DTS: _____

OPERATIVE REPORT

PATIENT: _____
ROOM NO: _____
DATE OF SURGERY: _____

MEDICAL RECORD NO: _____
CASE NO: _____
SURGEON: _____
ASSISTANT: _____

- PREOPERATIVE DIAGNOSES:
1. Left lower quadrant pain.
 2. Stress urinary incontinence.

- POSTOPERATIVE DIAGNOSES:
1. Adhesions of gut and omentum to the left pelvic sidewall and left ovary.
 2. Stress urinary incontinence.

- NAME OF OPERATION:
1. Exploratory laparotomy.
 2. Bilateral salpingo-oophorectomy.
 3. Adhesiolysis.
 4. Marshall-Marchetti-Krantz procedure.

ANESTHESIA: General anesthesia

DESCRIPTION OF PROCEDURE:
Under general anesthesia, the patient was placed in the supine position. A #16-French Foley catheter with a 30 cc bulb had been inserted into the bladder prior to prepping and draping.

A Pfannenstiel skin incision was made, carried down through the subcutaneous fat which was then entered sharply and incised to the transverse fascia and elevated away from the rectus muscle. The rectus muscle was then split in the midline and the anterior peritoneum identified and incised vertically, and an O'Connor-O'Sullivan retractor was used to expose the pelvis. The intimate adherence of the gut to the left pelvic sidewall completed hid the left ovary which was also intimately adherent to the left pelvic sidewall. With meticulous fine dissection with Metzenbaum scissors and also by teasing with a DeBakey forceps, and the use of needle point Bovie, the area was freed up until the left infundibulopelvic ligament was identified as was the ureter and the left pelvic sidewall. The left ovary was clamped across the infundibulopelvic ligament, transected and removed, and #0 Vicryl tie was used to secure this ligament.

Inspection of the pedicle row after intensive meticulous dissection of adhesions had caused retroperitoneal exploration of the ureter and vessels were all appearing normal.

Continued...

B 209
CENTER 26
PATIENT 6

OPERATIVE REPORT

Reperitonealization was accomplished by the used of #2-0 Vicryl and then a small pledget of Interceed was placed over the area of gut which had been taken off of the left pelvic sidewall and ovary.

The right ovary also had some adhesions and this was freed with needle point Bovie dissection along with Metzenbaum scissors dissection, and adhesiolysis of this area allowed the right infundibulopelvic to be clamped, transected, and suture ligated with #0 Vicryl. Following this, no active bleeding being seen, the peritoneum was closed and the procedure was continued in the space of Retzius where the Foley bulb and catheter were manipulated by the circulating nurse to assure the bulb's placement at the urethrovesical junction. Then a Babcock clamp was used to grasp the Foley tube passed the bulb at the urethrovesical junction and elevating the urethra two stitches of #1 chromic were placed on either side of the urethra in the periurethral fascia. Then, using half circle trocar needles, these four sutures were tacked to the posterior portion of the pubic symphysis, tied down with elevation of the urethrovesical angle without difficulty.

The Foley catheter was then deflated and removed. It was inspected to make sure that it was intact and did so appear and then the fascia was then closed with #0 vicryl after inspection revealed no active bleeding. The subcutaneous fat was reapproximated with running #2-0 plain and the skin was closed with #3-0 Monocryl. Benzoin was then placed on the skin and Steri-Strips were placed across the incision.

The patient tolerated the procedure well. Estimated blood loss was less than 50 cc. The patient returned to the recovery area in satisfactory condition. The sponge and needle counts were reported as correct times two at the end of the procedure.

209

CT PELVIS. 4671/20/97

CENTER 26

PATIENT 6

P: 61708/97
T: 04/20/97
JUN 2 1998

0710

CLINICAL HISTORY: SEVERE LEFT LOWER QUADRANT PAIN RADIATING TO THE LEFT HIP.

CT SCAN OF THE PELVIS:
FINDINGS: THE INCLUDED SOFT TISSUE ORGANS APPEAR UNREMARKABLE.
THERE IS NO MASS LESION IDENTIFIED.

IMPRESSION: NO SIGNIFICANT RADIOGRAPHIC ABNORMALITY SEEN.

RADIOLOGIST: _____

PATIENT NAME:
LOC:
ACCT:
MRN:

AGE: 046 SEX: F
TYPE: I

WD
AT

R

B 209
CENTER 26
PATIENT 6

NEW PATIENT HISTORY & PHYSICAL

DOCTOR: _____ DATE: 09/09/97 M.B.W.D.: M
NAME: _____ PATIENT NO.: _____ AGE: 46
ADDRESS: _____
PHONE #: _____ BIRTH DATE: 5/17/51 REFERRED BY: Sister

LABORATORY:

USUAL WT: 128 lb. PRESENT WT: 131 lb. HT: 5'0"
BP: 130/78 LMP: Hyst. (Premarin) HCT: 9/97
SUA: _____ HEMOCULT: _____ PAP: _____
SMEAR: _____ MAMMO: 1996 VS CHOL: 9/97

CHIEF COMPLAINT:

Left lower quadrant pain of two weeks' duration.

HISTORY OF PRESENT ILLNESS:

This patient is a 46-year-old white female who had a hysterectomy in 1979 because of excessive bleeding. She had acute onset of left lower quadrant pain about two weeks ago and was seen in the _____ where she had consultations by gastroenterology, surgery, and gynecology. The patient subsequently had CT scans of the pelvis, abdomen, ultrasound of the pelvis, and a barium enema, all of which were inconclusive. She was told that the most likely scenario was that she had adhesions. The patient has had a consistent burning-twisting type pain which has caused her to miss work and which is continuing to cause her extreme discomfort. The patient takes Premarin 0.625 daily and has been on this for the past year. She also has some problems with stress urinary incontinence, particularly when she is trying to do aerobics or jazzercise, and with coughing or sneezing. This has also been present for approximately one year. The patient denies any other symptoms and has brought with her today pictures of her ultrasound, barium enema, and CT scans.

She desires to correct this situation and is here because she has not been able to get any definite resolution for her problem.

REVIEW OF SYSTEMS:

The patient has had reflux esophagitis since 1994. She takes Pepcid when necessary.

SOCIAL HISTORY:

She denies the use of tobacco, ethanol, street drugs, or the presence of tattoo. She is at increased AIDS risk. She works in surgery with Dr. _____

Novartis Pharmaceuticals
Corporation
59 Route 10
East Hanover, NJ 07936

facsimile transmittal

To: _____ Fax: 918-743-7408

From: _____ Date: 03/13/00

Re: Study 209: Patient 26-06 Pages: 7

CC: Pat Riggio

Urgent For Review Please Comment Please Reply Please Recycle

Following please find a copy of patient 26-06's (protocol 209) H&P, operative report and discharge summary that was submitted to us by your site. A SAE of "ovarian cyst" was reported for this patient. We have reviewed the reports and have not found mention of "ovarian cyst" only "adhesions".

Change to adhesions not cyst. 3/20/00

Could you and _____ re-review this patient's case to determine if the diagnosis of this event is "ovarian cyst"?

*For
faking
note about
adhesions*

Thank you in advance for your prompt attention to this matter.
Best regards,

CONFIDENTIAL

13209/26/6

NOVARTIS CHFT919-209

MARCH 21, 2000

MEMO TO FILE

After reviewing post operative reports, diagnosis confirmed as adhesions to vaginal wall rather than ovarian cysts. Permission for Novartis to change SAE from ovarian cyst to vaginal adhesions.



Study/Patent identity B209/028/0004

Sex, age, race: female, 36yr, Caucasian

Past history: penicillin allergy, sinus congestion, myositis, hiatal hernia, urinary tract infection, cervical conization (stage CIN3). Likely ovarian cysts & uterin adenomyosis on previous CT and US scans.

Summary case history: **hysterectomy + R-salpingo-oophorectomy for uterin adenomyosis & ovarian cyst**

The patient began treatment in this 12 month, open-label study on 3Feb 1997

In July 1996, seven months before entering the study, she had undergone a diagnostic work-up for abdominal pain (CT scan: "low attenuation within adnexal areas suggestive of ovarian cysts"; US scan according to subsequent surgical admission report had showed "diffusely inhomogeneous uterin texture with suspected adenomyosis").

During the course of the study, she presented with pelvic pain and severe dysmenorrhea. Towards the end of the study she underwent surgery with hysterectomy + R-salpingo-oophorectomy on 5 Dec 97 (day 306). The pathology report describes large (diameter 3.5cm), thin-walled, partially luteinized follicle cyst and scattered small cysts in the remainder of the R-ovarian cortex together with focal superficial adenomyosis of the uterus. Study medication was uninterrupted and the patient completed the study. The investigator considered the episode to be unrelated to the study drug.

Attachments: CT scan report (Jul96); serious adverse report from investigator (Dec97); hospital admission history & physical, operative reports; discharge summary; extract from pathology report (Dec97).

Accessory information (from case record form):

Study medication administration

Medication	Dosage (mg/d)	Dates
tegaserod	4	3Feb - 3Mar97
	12	3Mar - 30 May97
	12	1Jun97 - 9Jan98

Prior/Comedication

Medication (route)	ATC class	Dates
Dicycloverine hydrochloride (oral)	Synthetic anticholinesterase	Prior (Aug96) - 26Jan97
Paracetamol (oral)	Anilides	17 - 26Apr97
Mylanta (oral)	Anatacid + antifatulent	8 - 11Nov97
Methocarbamol (oral)	Carbamic acid ester	4Feb - 14Mar97
Bactrim (oral)	Sulfonamide + trimethoprim	4-11Feb97, 17-26Apr97
Phillips laxcaps (oral)	Contact laxative	17Feb, 11Aug, 17Aug97
Beclometasone dipropionate (nasal)	corticosteroid	17Apr-16Sep97, 20Nov97 - cont.
Cough/cold preparation	Cough/cold preparation	14-15Apr97
Triamcinolone acetonide (nasal)	glucocorticoid	16Sep-18Nov97
Mepergan (oral)	Phenylpiperidine derivatives	20Nov-12Dec97
Naproxen sodium (oral)	Propionic acid derivative	4-22Feb97, 13-16Sep97, 1-5Nov97
Pseudonephrine hydrochloride (oral)		20Nov97 - cont.

All reported adverse events

Event	severity	Dates	Relationship*
Flu-like symptoms	moderate	14-26Apr97	unlikely
pain	moderate	5-12Dec97	unrelated

Event	severity	Dates	Relationship*
Abdominal pain	moderate	14Oct97	unlikely
Flatulence	moderate	8-11Nov97	unlikely
Nausea	mild	3-6Feb97	probably
	moderate	14Oct97	unlikely
Arthropathy	moderate	12-16Sep97	unrelated
Back pain	Mild/severe	25May-6Dec97	unlikely
Ovarian cyst	moderate	5Dec97	unrelated

* relationship with study medication as assessed by investigator

SDZ HTF 919 Study Code: HTFB 209-E-00	ID	28 <small>centre no</small>	A <small>subject no</small>	SAE
	Subject's initials			
	Date of report	12 <small>month</small>	18 <small>day</small>	197 <small>year</small>

SERIOUS ADVERSE EVENT REPORT

*See attached Instruction Sheet for information on completion of SAE Form.
In addition, complete the ADVERSE EVENTS FORM

Date of birth: 03 | 28 | 61
month day year

Weight: 137
lb

Height: 68
in

Sex: Male Female

Race: Caucasian Black Asian/Oriental

Pregnant: Yes No Not Applicable

Other (specify): _____

Relevant medical history: LEEP PROCEDURE 1993

ADVERSE EVENT specify as reported on AE form:

Clinical description (incl. diagnosis): OVARIAN TUMORS, HYSTERECTOMY

Reason for reporting

Requires or prolongs hospitalization Cancer Life-threatening Death

Persistently disabling or incapacitating Congenital anomaly Overdose

Other (specify): _____

Start date: 12 | 05 | 97 month day year Start time: _____ : _____ 24 hr clock

End date: 12 | 05 | 97 month day year End time: _____ : _____ 24 hr clock

Relevant findings (e.g. ECG, autopsy, lab data, incl. copies of lab sheets)

Therapeutic measures: HYSTERECTOMY

Course and outcome _____

HTFB/209/0/28/4/1/USA
HTFB-209-28-004



SDZ HTF 919 Study Code: HTFB 209-E-00	ID <u>28</u> <u>4</u> <small>CENTRE NO SUBJECT NO</small>	SAE
	Subject's initials _____	

SERIOUS ADVERSE EVENT REPORT

In addition, please complete the 'ADVERSE EVENTS' form

STUDY MEDICATION

Daily dose 12 mg

Start date of medication 02/03/97
MONTH DAY YEAR

Route of administration PO

Time elapsed between last drug administration and onset of event _____

Dose reduction because of event No Not Applicable Yes → Date _____
month day year

Discontinuation because of event No Yes → Date _____
month day year

Code broken No Not Applicable Yes → Name of drug received _____

CONCOMITANT MEDICATION

Drug name	Indication	Daily dose at time of event	Route of administration	Start date	End date

ASSESSMENT OF CAUSALITY

Event causality Study indication Concomitant therapy Other, specify _____
 Coexistent medical condition Study medication

Relationship to study medication Not related Unlikely Possibly Probably Definitely

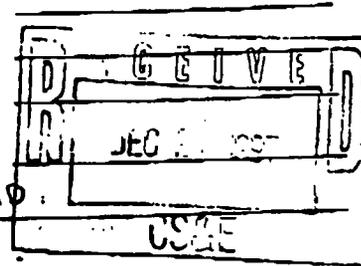
Justification of assessment given in Assessment of Causality
(e.g. study indication, coexistent medical condition, concomitant therapy, study medication, other)

Additional remarks HTFB/209/0/28/4/1/USA
HTFB-209-28-004

Institution _____

Investigator's name (please print) RON PRUITT, M.D.

Investigator's signature _____



RUN ON 07/11/96-1356

RADIOLOGY REPORT

JEP 03/28/61 35 ACCT #
LOC

PATIENT STATUS: SDC

RE: _____, CT/CT ABDOMEN W/CONTRAST, _____ CT/CT LIMITED SCAN
EXAM DATE: 07/10/96 ORDERED BY: _____

REPORT STATUS: DRAFT (not yet signed) REPORTED BY: _____

ABDOMEN AND PELVIS CT WITH CONTRAST:

Clinical History: Abdominal pain.

TECHNIQUE: Images obtained on a GE High Speed Advantage Helical CT scanner. 7 mm axial sections at 7 mm intervals obtained helically from the diaphragm to just caudal to the kidneys. 10 mm axial sections at 10 mm intervals obtained through the lower abdomen and pelvis non-helically. Oral and mechanically injected nonionic intravenous contrast used.

FINDINGS: The lung bases are clear. No pleural fluid identified. The liver and spleen are of homogeneous attenuation. The pancreas appears of normal size and configuration. The kidneys are of normal configuration, without obstruction. There is no evidence of retroperitoneal or pelvic lymphadenopathy or mass. Regions of low attenuation seen within the right and left adnexal areas, most likely ovarian cysts. The left ovary is somewhat prominent. Correlative ultrasound may be helpful for complete evaluation. No definite free peritoneal fluid.

IMPRESSION: PROBABLE OVARIAN CYST. THE LEFT OVARY APPEARS SOMEWHAT PROMINENT. CORRELATIVE ULTRASOUND WOULD BE HELPFUL FOR COMPLETE EVALUATION, IF CLINICALLY INDICATED. CT OF THE ABDOMEN OTHERWISE WITHIN NORMAL LIMITS.

OVARIAN CYST
NEVER
DIAGNOSED

TRANSCRIBED DATE/TIME: _____
TRANSCRIPTIONIST: _____

FOR EXAM: _____ CT/CT ABDOMEN W/CONTRAST
CAMPUS: _____

How is patient transported? A - AMBULATORY
Is patient on isolation? N
Is patient pregnant? N
Reason for procedure?
Comments: PT HERE

FOR EXAM: _____ CT/CT LIMITED SCAN
CAMPUS: _____

How is patient transported? A - AMBULATORY
Is patient on isolation? N
PAGE 1 COPY

(CONTINUED)

B209 ZELMAC
Center 28
PATIENT 4

RUN ON 07/08/96-1337

RADIOLOGY REPORT

K F 03/88/61 35 ACCT
LOC:

PATIENT STATUS: OUT

RE: US/US ABDOMEN
EXAM DATE: 07/08/96

ORDERED BY:

REPORT STATUS: DRAFT (not yet signed) REPORTED BY:

Ultrasound examination of the upper abdomen shows a gallbladder that is normal in size and shape. Its walls are of normal thickness. No stones are seen. Common bile duct is normal in diameter. Biliary tree is not dilated. Liver, spleen, pancreas, aorta and both kidneys are well visualized and appear to be within normal limits.
IMPRESSION: . NCRMAL ABDOMINAL ULTRASOUND.

CC:

TRANSCRIBED DATE/TIME: 07/08/96 (1200)
TRANSCRIPTIONIST:

FOR EXAM: US/US ABDOMEN
CAMPUS:

- How is patient transported? S - STRETCHER
- Is patient on isolation? N
- Is patient pregnant? N
- Reason for procedure? R/O GALLSTONES
- Comments:

B209 - ZELMAC
Center 28
Patient 4

NAME:
MED REC NO.:
ADM DATE:
ATTENDING:
DICTATING:
DICTATE DATE: 12/03/97
ROOM NO:
PATIENT ACCT NO.:

HISTORY AND PHYSICAL

REQ NO. 1

cr

PREADMISSION HISTORY AND PHYSICAL: This patient is scheduled to be an early morning admission on December 5, 1997.

ADMITTING DIAGNOSIS:
1. Adenomyosis.

HISTORY: This is a 36-year-old female who is admitted with a history of severe dysmenorrhea and pelvic pain and with a history of periods every two weeks. The patient's periods last approximately five days and has symptoms of menorrhagia. The patient is unable to take oral contraceptives. She also has a past history of having had a cold knife conization which revealed CIN-III of the cervix. The patient is now admitted for a total abdominal hysterectomy. The patient has had previous CT scan which had revealed a left ovarian cyst and an enlarged uterus. Her ultrasound on 07/26/96 revealed a diffusely inhomogeneous uterine texture with suspected adenomyosis.

PAST HISTORY: Surgery - Cold knife conization. No history of tuberculosis, diabetes, rheumatic fever or asthma. She does have a history of spastic colon.

SOCIAL HISTORY: She smokes one-half a pack of cigarettes daily.

MEDICATIONS: None.

ALLERGIES: PENICILLIN, CODEINE AND ASPIRIN.

PHYSICAL EXAMINATION:

VITAL SIGNS: Weight is 133 pounds, blood pressure is 90/60.

HEENT: within normal limits.

CARDIOVASCULAR: Regular sinus rhythm without murmur.

ABDOMEN: Soft without tenderness.

CONTINUED...

HISTORY AND PHYSICAL

B209 ZELMAC
CENTER 28
PATIENT 4

NAME:
MED REC NO.:
ADM DATE:
ATTENDING:
DICTATING:
DICTATE DATE: 12/03/97
ROOM NO:
PATIENT ACCT NO

HISTORY AND PHYSICAL

REQ NO.:

PAGE 2

GENITOURINARY: The pelvic examination shows the cervix within normal limits. The Pap smear on 07/29/96 was normal. There was one on 10/16/97 was of undetermined significance but primarily due to degenerative cells. The uterus was retroflexed, tender, boggy. The adnexa were without masses.

IMPRESSION:

1. Post cold knife conization for CIN-III.
2. Adenomyosis.

PLAN: Total abdominal hysterectomy.

D: 12/03/97
T: 12/03/97
00
Time Dictated: 16:34

DICTATED BY:
REVIEWED BY

HISTORY AND PHYSICAL

B209 ZELMAC
CENTER 209
PATIENT 4
TOTAL P.09

NAME:

MED REC NO.:

ADM DATE:

ATTENDING:

SURGEON:

OPERATION DATE: 12/05/97

ROOM NO:

PATIENT ACCT NO.:

OPERATION REPORT

REQ NO.:

cc

PREOPERATIVE DIAGNOSIS:

1. Adenomyosis.

POSTOPERATIVE DIAGNOSIS:

1. Adenomyosis with right ovarian cyst.

OPERATION:

1. Total abdominal hysterectomy and right salpingo-oophorectomy.

SURGEON:

FIRST ASSISTANT:

PERTINENT FINDINGS AND OPERATIVE PROCEDURE: The patient was prepped and draped in the usual manner under general anesthesia. A Pfannenstiel incision was carried down through the skin, and fascia and peritoneum were incised. Self-retaining retractor was put in place. The uterus was boggy. There was about a 4.0 x 5.0 cm, most likely hemorrhagic corpus luteum of the right ovary. No evidence of endometriosis. The left ovary was normal, so it was decided best to proceed with total abdominal hysterectomy and right salpingo-oophorectomy. The uterus was grasped with a double-toothed tenaculum. The right round ligament was grasped with vanderbilts, incised, and carried down inferiorly with #1 Chromic suture. The right infundibulopelvic ligament was doubly clamped with curved Heaney's, incised, sutured ligatured with #1 Chromic and free tied with #1 Chromic. A similar procedure was performed on the left, clamping the left utero-ovarian ligament. The bladder was dissected sharply and bluntly off the cervix. Skeletonization was accomplished bilaterally. The right uterine vessels were grasped with curved Heaney's, incised, suture ligatured with #1 Chromic and free tied with #1 Chromic. The same procedure was performed for the left uterine vessels. The right cardinal and uterosacral ligaments were grasped with straight Heaney's, incised, suture ligatured with #1 Chromic. The same procedure was performed for the left cardinal and uterosacral ligaments. The vagina was entered on the right side and angle sutured with #1 Chromic. The same procedure was performed for the left angle. Specimen was removed.

CONTINUED...

OPERATION REPORT

B209 ZELMAC
CENTER 28
PATIENT 4

NAME:
MED REC NO.:
ADM DATE:
ATTENDING:
SURGEON:
OPERATION DATE:
ROOM NO:
PATIENT ACCT NO.:

OPERATION REPORT

SEQ NO.:

PAGE 2

The cuff was closed with interrupted #1 Chromic suture. Hemostasis was adequate. Irrigation was done. The self-retaining retractor was removed. Lap count was correct. The peritoneum was closed with a 0 Monocril, PDS x two for the fascia, and staples for the skin.

D: 12/05/97

T: 12/05/97

37

Reviewed by

DICTATED B.

OPERATION REPORT

B209 ZELMAC
Center 28
Patient 4

12/27/97 18:17

SERV: GYNECOLOGY
DIAG: ADENOMYOSIS
ISOL: UNIVERSAL

MR#: _____
ADM: _____
DOB: 03/28/81
TYP: 1

ACCT#: _____
OIS: 12/08/97
AGE: 36 SEX: F
LOC: REAC

DISCHARGE SUMMARY

-PERMANENT CHART COPY-

REQ#

DISCHARGE SUMMARY

PHYSICIANS:

ATT: _____
REF: NO REF MD

ADM _____
CON: NONE

ORDER: DISCHARGE SUMMARY 182.01

AUTHOR: _____

182.01
DISC. DATE: _____

CC: _____

FINAL DIAGNOSES:
1. ADENOMYOSIS.

PROCEDURE: 12/5/97 - TOTAL ABDOMINAL HYSTERECTOMY, RIGHT SALPINGO-OOPHORECTOMY.

SUMMARY: THIS 36-YEAR-OLD FEMALE WAS ADMITTED WITH A HISTORY OF SEVERE DYSMENORRHEA AND PELVIC PAIN AND WITH A HISTORY OF PERIODS EVERY TWO WEEKS. THE PATIENT'S PERIODS LASTED APPROXIMATELY FIVE DAYS AND HAD SYMPTOMS OF MENORRHAGIA. SHE WAS UNABLE TO TAKE ORAL CONTRACEPTIVES. SHE ALSO HAD A PAST HISTORY OF HAVING HAD A COLD KNIFE CONIZATION WHICH REVEALED CIN III OF THE CERVIX. THE PATIENT WAS NOW ADMITTED FOR A TOTAL ABDOMINAL HYSTERECTOMY. SHE HAD PREVIOUS CT SCAN WHICH HAD REVEALED A LEFT OVARIAN CYST AND A LARGE UTERUS. HER ULTRASOUND ON 7/26/96 REVEALED A DIFFUSELY INHOMOGENEOUS UTERINE TEXTURE WITH SUSPECTED ADENOMYOSIS.

PAST HISTORY: COLD KNIFE CONIZATION. HISTORY OF A SPASTIC COLON.

ALLERGIES: PENICILLIN, CODEINE, ASPIRIN.

CURRENT MEDICATIONS: NONE.

PHYSICAL EXAMINATION: REVEALED THE PELVIC EXAM SHOWED THE CERVIX WITHIN NORMAL LIMITS. PAP SMEAR 7/29/96 WAS NORMAL. THERE WAS ONE ON

CONTINUED

DISCHARGE SUMMARY (X.XX)

B209 ZELMAC
CENTER 28
PATIENT 4

12/27/97 16:17

SERV: GYNECOLOGY
 DIAG: ADENOMYOSIS
 ISOL: UNIVERSAL

MR#: _____
 ADM: _____
 DOB: 03/28/61
 TYP: 1

ACCT#: _____
 DIS: _____
 AGE: 36 SEX: F
 LOC: REAC

DISCHARGE SUMMARY

-PERMANENT CHART COPY-

REQ#: _____

10/16/97 OF UNDETERMINED SIGNIFICANCE, BUT PRIMARILY DUE TO DEGENERATIVE CELLS. THE UTERUS WAS RETROFLEXED, TENDER, BOGGY. ADNEXA WITHOUT MASS.

LABORATORY VALUES: HEMATOCRIT 40. POTASSIUM 3.6.

HOSPITAL COURSE: ON ADMISSION TO THE HOSPITAL, THE PATIENT WAS PREPARED FOR THE PROCEDURE. RISKS AND BENEFITS WERE EXPLAINED TO HER. SHE UNDERSTOOD AND AGREED. SHE WAS TAKEN TO THE OPERATING ROOM ON 12/5, WHERE SHE UNDERWENT A TOTAL ABDOMINAL HYSTERECTOMY, RIGHT SALPINGO-OOPHORECTOMY UNDER GENERAL ANESTHESIA. PATHOLOGY REPORT SHOWED THE UTERINE CERVIX SHOWING PATCHY CHRONIC INFLAMMATION, CERVICITIS, IN ASSOCIATION WITH FOCAL CERVICAL SCARRING/DISTORTION COMPATIBLE WITH A PRIOR CONIZATION, FOCAL REACTIVE SQUAMOUS METAPLASIA, NO RESIDUAL DYSPLASIA IDENTIFIED, SECRETORY PATTERN ENDOMETRIUM, FOCAL SUPERFICIAL ADENOMYOSIS, UNREMARKABLE MYOMETRIUM AND SEROSA, OVARY AND FALLOPIAN TUBE ON THE RIGHT SHOWED OVARIAN 3.5 CENTIMETER PARTIALLY LUTEINIZED FOLLICLE CYST, UNREMARKABLE FALLOPIAN TUBE.

POSTOPERATIVE COURSE: THE PATIENT WAS PLACED ON IV FLUIDS. SHE WAS ON THE CARE PATH. SHE RAN A LOW GRADE FEVER. EFFORTS WERE MADE AT GOOD PULMONARY TOILET. HER ACTIVITY LEVELS WERE GRADUALLY INCREASED. WHEN HER BOWELS BEGAN TO FUNCTION, HER DIET WAS ADVANCED, AMBULATORY STATUS WAS RESUMED. THE WOUND LOOKED FINE. SHE DID HAVE SOME PROBLEMS WITH URINARY RETENTION, BUT THEN WAS VOIDING WITHOUT DIFFICULTY.

HER DIET WAS ADVANCED. ACTIVITY LEVELS WERE INCREASED. SHE WAS ABLE TO VOID AND HAVE BOWEL MOVEMENTS. SHE WAS DISCHARGED TO BE FOLLOWED AS AN OUTPATIENT.

AT THE TIME OF RELEASE FROM THE HOSPITAL, SHE WAS AFEBRILE. THE REMAINING VITAL SIGNS WERE WITHIN NORMAL LIMITS. LAST RECORDED HEMATOCRIT 33.7. SHE WAS AMBULATORY. SHE WAS INSTRUCTED ON LIMITED ACTIVITY, PREADMISSION DIET, GIVEN PRESCRIPTIONS AND COMPLETE INSTRUCTIONS ON TAKING MEPERGAN P.R.N. FOR PAIN AND RETURN TO THE OFFICE ON 12/10 FOR STAPLE REMOVAL OR SOONER IF NEEDED FOR FOLLOW-UP CARE.

 DICTATED BY
 REVIEWED BY

CONTINUED

DISCHARGE SUMMARY (X.XX)

B209 ZELMAC
CENTER 28
PATIENT 4

12/27/87 16:17

PAGE 003

SERV: GYNECOLOGY
DIAG: ADENOMYOSIS
ISOL: UNIVERSAL

MR#: _____
ADM: _____
DOB: 03/28/81
TYP: 1

ACCT# _____
DIS: _____
AGE: 36 SEX: F
LOC: REAC

DISCHARGE SUMMARY

-PERMANENT CHART COPY-

REC#: _____

MEDIFAX DOCUMENT
DICTATION TERMIN

LAST PAGE

DISCHARGE SUMMARY (X.XX)

B209 ZELMAC
CENTER 28
PATIENT 4

SURGICAL PATHOLOGY REPORT

Name: _____
MR # _____
Age/Sex: _____
SSN: _____
Date of Operation: 12/05/97
Date Reported: December 6, 1997
Physician(s): _____

Accession #: _____
Acct #: _____
DOB: 03/28/1961
Room: GYN77148

B 209 ZELMAC
CENTER 28
PATIENT 4

Clinical History: ADENOMYOSIS

FINAL DIAGNOSIS:

UTERUS, RIGHT OVARY AND FALLOPIAN TUBE; HYSTERECTOMY, RIGHT SALPINGO-OOPHORECTOMY:

- A. UTERUS
- 1) UTERINE CERVIX - PATCHY CHRONIC INFLAMMATION/CERVICITIS IN ASSOCIATION WITH FOCAL CERVICAL SCARRING/DISTORTION - COMPATIBLE WITH PRIOR CONIZATION - FOCAL REACTIVE SQUAMOUS METAPLASIA - NO RESIDUAL DYSPLASIA IDENTIFIED (SEE MICROSCOPIC).
 - 2) SECRETORY PATTERN ENDOMETRIUM - FOCAL SUPERFICIAL ADENOMYOSIS.
 - 3) UNREMARKABLE MYOMETRIUM AND SEROSA.
- B. OVARY AND FALLOPIAN TUBE (RIGHT) - OVARIAN 3.5 CM PARTIALLY LUTEINIZED FOLLICLE CYST; UNREMARKABLE FALLOPIAN TUBE.

GROSS DESCRIPTION:

Received is a single specimen designated "uterus, right tube and ovary". The right fallopian tube measures 6 cm in length and 5 mm in greatest diameter. The fimbriated end is unremarkable. No focal lesions are present. The associated ovary is tan-pink to red-brown in color and measures 5 cm in greatest dimensions. The external surface varies from glistening to granular to mildly convoluted. The ovary is cystic in character and hemorrhagic over an area measuring roughly 4.5 x 4 cm in greatest dimensions. Sectioning of the ovary demonstrates a large thin walled cyst filled with hemorrhagic serous fluid. The cyst measures approximately 3.5 cm in greatest dimensions. The cyst lining is glistening without focal lesions. The remainder of the ovarian cortex demonstrates scattered small cortical cysts as well as corpora albicantia. No additional changes are noted. Four sections including ovary and tube are submitted in two cassettes A and B (3/1, 2/1)

The uterus weighs 55 grams and measures 8 x 5 x 4 cm in greatest dimensions. The uterus is pear shaped in configuration. The serosa overlying the uterine body and fundus is tan-pink in color and glistening without focal lesions. The cervical portion of the uterus externally exhibits rough irregular fibrous and fibromuscular soft tissue without focal lesions. The cervical os is linear and measures 8 mm in length. Ectocervical mucosa is tan-pink in color and glistening. The endocervical canal measures approximately 2 cm in length. The mucosa is tan-

B209/28/4 ✓

SURGICAL PATHOLOGY REPORT

Name: _____
MR #: _____
Age/Sex: _____
SSN: _____
Date of Operation: 12/05/97
Date Reported: _____
Physician(s): _____

Accession #: _____
Acct #: _____
DOB: 03/28/1961
Room: GYN77148

B 209 EdMA
Center 28
PATIENT 4

Clinical History: ADENOMYOSIS

FINAL DIAGNOSIS:

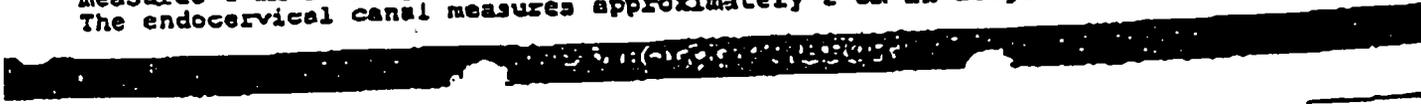
UTERUS, RIGHT OVARY AND FALLOPIAN TUBE; HISTERECTOMY, RIGHT SALPINGO-OOPHORECTOMY:

- A. UTERUS
 - 1) UTERINE CERVIX - SAICHY CHRONIC INFLAMMATION/CERVICITIS IN ASSOCIATION WITH FOCAL CERVICAL SCARRING/DISTORTION - COMPATIBLE WITH PRIOR CONIZATION - FOCAL REACTIVE SQUAMOUS METAPLASIA - NO RESIDUAL DYSPLASIA IDENTIFIED (SEE MICROSCOPIC).
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Study/Patent identity B307/721/0002

Sex, age, race: female, 37yr, Caucasian

Past history: breast fibrocystosis, two miscarriages (94,95), hysterectomy (fibroids), knee tendinitis

Summary case history: **R-salpingo-oophorectomy, appendicectomy & lysis of adhesions for R-abdominal pain. Adhesions & peritubal cyst at pathology.**

The patient began treatment in this double-blind study on 16Feb1998, receiving tegaserod 4mg/d which was increased to 12mg/d on 23May99.

She experienced R-abdominal pain on day 75 and was hospitalized for severe umbilical pain, radiating to R-lower quadrant reported on day 86. A one week work-up concluded at mild peritonitis + small ovarian cyst believed to have ruptured leading to some improvement and she was discharged for outpatient follow-up only. Treatment with danocrine was started later for recurrence of the cyst but with persistence of her pain she was readmitted on 8Jul98 (3weeks after completion of study) for exploratory laparotomy. She underwent R-salpingo-oophorectomy, lysis of pelvic adhesions and appendicectomy. Subsequent pathology showed R-ovarian and fallopian serosal adhesions, peritubal cyst with no evidence of endometriosis and normal appendix.

Attachments: original serious adverse event report from investigator; hospital discharge notes; pathology report.

Accessory information (from case record form):

Study medication administration

Medication	Dosage (mg/d)	Dates
tegaserod	4	16Feb98 - 23Mar98
	12	23Mar98 - 19May98

Prior/Comedication

Medication (route)	ATC class	Dates
Mg citrate (oral)	Osmotic laxative	Prior (1990)
Danocrine (oral)	antigonadotrophins	Prior (15.21Jan98)
Macrobid (oral)	nitrofurans	3-9 Feb-98
Naproxen (oral)	Propionic acid derivative	2-17 Mar 98
Fleet enema (oral??)	enema	17Mar98

All reported adverse events

Event	severity	Dates	Relationship*
Sharp R-abdominal pain	moderate	1-3May98	possibly
Stomach cramps	severe	12May98	possibly
constipation	moderate	17Mar98	possibly
R-ovarian cyst	severe	26May-8Jul98	unlikely

* relationship with study medication as assessed by investigator

SDZ HTF 919

Study Code: HTFB 307-E-00

ID 721 02
center no. subject no.

Subject's initials

Date of report 27 MAY 98
day month year

SAE Report

SERIOUS ADVERSE EVENT REPORT

Page 1 / 2

*See attached Instruction Sheet for information on completion of SAE Form.
In addition, complete the ADVERSE EVENTS FORM

Date of birth 05 DOCT 60
day month year

Weight 114
lbs

Height 64
inches

Sex Male Female

Race Caucasian Black Asian/Oriental

Pregnant Yes No Not Applicable

Other (specify): _____

Relevant medical history hysterectomy (1979)

ADVERSE EVENT specify as reported on AE form:

Clinical description (incl. diagnosis) Right lower quadrant pain. CT scan shows 2.7 cm excision cyst on right ovary

Reason for reporting

- Requires or prolongs hospitalization
- Cancer
- Life-threatening
- Death
- Persistently disabling or incapacitating
- Congenital anomaly
- Overdose
- Other (specify): _____

Start date 26 MAY 98 Start time _____ End date _____ End time _____
day month year 24 hr. clock day month year 24 hr. clock

Relevant findings (e.g. ECG, autopsy, lab data, ind. copies of lab sheets)

HTFB/307/0/721/2/1/USA
HTFB-307-721-002

Therapeutic measures _____

Course and outcome Yet to be determined. Currently condition is on going.

28 MAY 1998

HISTORY & PHYSICAL MR#
LOC: SSN#

DOB: 10/5/60

ADMIT DATE:
DISCHARGE DATE:

CHIEF COMPLAINT: ABDOMINAL PAIN.

HISTORY OF PRESENT ILLNESS: THE PATIENT IS A 37 YEAR OLD MARRIED BLACK FEMALE, PARA II, PREVIOUS TAH FOR FIBROIDS, WHO IS ADMITTED BECAUSE OF PERSISTENT ABDOMINAL PAIN. THIS PATIENT WAS ADMITTED WITH UNEXPLAINED ABDOMINAL PAIN APPROXIMATELY SIX WEEKS AGO AND WAS HOSPITALIZED FOR ABOUT ONE WEEK WITH PAIN THAT WAS SEVERE, PERIUMBILICAL WITH RADIATION TO THE RIGHT LOWER QUADRANT. HER WORK UP WAS BASICALLY NEGATIVE. SHE DID HAVE A SMALL OVARIAN CYST THAT WAS FELT TO HAVE RUPTURED AND RESOLVED. HER PAIN IMPROVED SOMEWHAT. SHE DID MAINTAIN AN ADEQUATE REGULAR DIET AFTER A FEW DAYS IN THE HOSPITAL BUT WAS SENT HOME WITH AN UNCERTAIN DIAGNOSIS OF UNEXPLAINED PERIUMBILICAL PAIN, MILD PERITONITIS, RUPTURED OVARIAN CYST. SHE HAS BEEN FOLLOWED AS AN OUTPATIENT SINCE THAT TIME THROUGH OUR OFFICE AND DR. ROBERTS AS SHE DOES HAVE AN IRRITABLE BOWEL, WHICH REMAINS UNDER TREATMENT. CONSIDERATION FOR SURGERY WAS DONE IN THE HOSPITAL IN CONSULTATION WITH DR. BUT IT WAS NOT FELT THAT THE PATIENT'S SITUATION WARRANTED A MAJOR OPERATION. SHE WAS SEEN AT STOVER OBGYN AND HAD RESUMPTION OF A SMALL RIGHT OVARIAN CYST. SHE WAS PLACED ON DANOCRINE, BUT THE PAIN PERSISTED AND SHE IS NOW BEING ADMITTED FOR EXPLORATORY LAPAROTOMY, REMOVAL OF THE RIGHT OVARY, POSSIBLE REMOVAL OF THE LEFT OVARY AND EVALUATION OF HER GI TRACT.

PAST MEDICAL HISTORY: ILLNESS SIGNIFICANT FOR IRRITABLE BOWEL SYNDROME. SURGERIES SIGNIFICANT FOR ABDOMINAL HYSTERECTOMY, THREE VAGINAL DELIVERIES, PRIOR COLONOSCOPY. SHE HAS HAD NO DIFFICULTY WITH ANESTHESIA IN THE PAST.

INDICATIONS: VICODIN FOR PAIN.

ALLERGIES: CODEINE AND TERRAMYCIN.

PAST HISTORY: MARRIED, NON-DRINKER, NON-SMOKER.

FAMILY HISTORY: NO BREAST OR GYN CANCER.

REVIEW OF SYSTEMS: HISTORY OF BREAST LUMPS, BENIGN. GI PROBLEMS ABOVE AND HER MOST RECENT CHRONIC PAIN PATTERN.

PHYSICAL EXAM:

GENERAL: SHE IS A LEAN BLACK FEMALE IN NO DISTRESS.

HISTORY & PHYSICAL MR#

Pt. No 721-2

 HISTORY & PHYSICAL MR# _____
 DB: 10/5/60 LOC: _____ SSN# _____

 VITAL SIGNS: WEIGHT 114, BLOOD PRESSURE 104/60, PULSE 72,
 RESPIRATIONS 12, AFEBRILE.

SENT: NO ABNORMALITIES.

CK: NO THYROMEGALY.

LUNGS: CLEAR TO AUSCULTATION.

HEART: NORMAL SINUS RHYTHM.

ABDOMEN: SOFT, FLAT, NO REBOUND, GUARDING OR MASSES. WELL HEALED PFANNENSTIEL INCISION.

EXTREMITIES: NO PERIPHERAL EDEMA.

NEUROLOGIC: INTACT.

PELVIS: VAG CLEAR. BUS CLEAR. VAGINA INTACT MUCOSA, GOOD COUPLAGE, CUFF WELL HEALED AND SUPPORTED. CERVIX AND UTERUS UNENLARGED. BIMANUAL REVEALS DIFFUSE ABDOMINAL TENDERNESS, WORSE ON THE RIGHT, NO MASS CAN BE APPRECIATED. RECTOVAGINAL CONFIRMS, GONORRHOEA NEGATIVE, ANUS CLEAR.

IMPRESSION: CHRONIC LOWER ABDOMINAL PELVIC PAIN WITH A HISTORY OF OVARIAN CYST AND IRRITABLE BOWEL SYNDROME.

PLAN: THE PATIENT IS ADMITTED FOR AN EXPLORATORY LAPAROTOMY BY _____ (SELF AND DR. _____). WE PLAN TO REMOVE THE RIGHT OVARY, CONSIDER REMOVAL OF THE LEFT OVARY PENDING OPERATIVE FINDINGS, AND TO EVALUATE THE BOWEL STRUCTURES AS BEST AS POSSIBLE. THE PATIENT WILL BE APPROACHED WITH A MIDLINE INCISION, WHICH WAS DISCUSSED THE DAY PRIOR TO SURGERY. SHE ALSO HAS TAKEN A GALLON OF GOLYTELY FOR BOWEL PREPPING. WE HAVE DISCUSSED THE RISK OF SURGERY TO INCLUDE INFECTION, BLOOD LOSS POSSIBLY REQUIRING TRANSFUSION, INJURY TO ADJACENT TISSUES, IF BOTH OVARIES ARE REMOVED ESTROGEN REPLACEMENT THERAPY WILL BE MANDATED, AND ANESTHESIA RISKS. QUESTIONS HAVE BEEN ANSWERED, INFORMED CONSENT OBTAINED. THE RISKS, BENEFITS AND ALTERNATIVES ARE REVIEWED.

 DICT: _____ TDICT: 17:10
 RID: _____ DTRAN: 07/15/98 TTRAN: 07:49 AM

 HISTORY & PHYSICAL MR# _____

Pt. No 721-2

 [REDACTED] DISCHARGE SUMMARY MR#
 DOB: 10/5/60 LOC: SSN#

ADMIT DATE: _____
 DISCHARGE DATE: _____

- DISCHARGE DIAGNOSES:
1. Chronic pelvic - abdominal pain.
 2. Right ovarian cyst.
 3. Pelvic adhesions.

- PROCEDURES: 7/8/98
1. General anesthesia.
 2. Exploratory laparotomy.
 3. Right salpingo-oophorectomy.
 4. Lysis of pelvic adhesions.
 5. Appendectomy.

ATTENDING PHYSICIAN: _____

CONSULTING PHYSICIAN: _____

COMPLICATIONS: None.

HISTORY: For the details, see the chart. In brief, the patient is a 37-year-old married black female, Para II, with previous abdominal hysterectomy for fibroids. She was admitted because of persistent abdominal pain. She had been hospitalized six weeks prior with severe periumbilical pain with radiation into the right lower quadrant and a negative work-up by Obstetrics/Gynecology, General Surgery and Gastrointestinal Services. She was eventually discharged with unexplained pain with some resolution. No evidence for bowel obstruction or an inflammatory process. She had a small ovarian cyst that had actually apparently ruptured during her hospital stay which was felt to possibly be contributing to some of her pain. This was negative resolved. She was discharged to home in good condition to be followed as an outpatient. She had several visits and was placed on Danocrine suppression which afforded minimal relief and the decision was then made to go ahead and admit her for laparotomy, bowel evaluation because she does have some irritable bowel history and to evaluate her adnexa which were already in place. She had a normal preoperative course.

 DISCHARGE SUMMARY MR#

14. No. 721-2

DISCHARGE SUMMARY MR#
LOC: SSN
DOB: 10/5/60

DDict: 08/04/98 TDict: 14:40
TrID: DTran: 08/12/98 TTran: 02:17 PM

cc:

Pt. No. 721-2

MR#

HOSPITAL COURSE: The patient was admitted in good condition for surgery on 7/8/98. With informed consent she was taken to the

operating room where exploratory laparotomy was performed through a midline incision. She had pelvic adhesions on the right around the adnexa. The right adnexa was removed as was the appendix. Adhesions were lysed. Dr. _____ was in attendance for the appendectomy and lysis of adhesions. The operative course was routine and without complications. Blood loss was 100 ccs. No evidence of endometriosis was noted at the time. Postoperative recovery was uneventful. She did not require bowel decompression with nasogastric suction and she eventually had resumption of bowel and bladder function. She was advanced to a diet slowly due to her fairly thorough bowel evaluation and appendectomy. By postoperative day number three she was advanced on to a regular diet which she tolerated and by postoperative day four she was doing very well. Her pain was under good control and she was afebrile. Her incision was healing. Physical examination was considered within normal limits.

The final pathology did show right ovarian and fallopian serosal adhesions, peritubal cyst, no evidence of endometriosis and the appendix showed no pathologic diagnosis.

Postoperative hemoglobin was 9.7 and she will was treated with iron only. She had stable vital signs. On postop day four she was considered stable and ready for discharge having reached maximal hospital benefit. She is discharged home to her family in good condition. She is to return to the office in three days for staple removal. She will call for incisional problems, bleeding or fever.

DISCHARGE MEDICATIONS:

1. Percocet.
2. Ibuprofen.
3. Multivitamins and iron.

FOLLOW-UP: In three days.

DISCHARGE SUMMARY

MR# _____

Pl. No. 721-2

Chart Number:
Patient:
Patient:
Fin #
Sex: F DOB: 10/05/60 Age: 37 YRS
Phone: () -
Admitting Physician:
Ordering Physician:
Copy to:

Printed: 07/10/98

SURGICAL PATHOLOGY

Collection Date : 07/08/98

Accession:

SPECIMEN:

A. PELVIC SIDE WALL BIOPSY; B. RIGHT TUBE AND OVARY; C. APPENDIX

PRE-OP INFORMATION:

Rule out endometriosis, abdominal pain

POST-OP INFORMATION:

Same, right ovarian cyst

GROSS DESCRIPTION:

A. The specimen is received fresh for frozen section and consists of a 0.7 x 0.6 x 0.1 cm. piece of pink-tan tissue without blood clot-areas or adhesions. All submitted for frozen section. The frozen section tissue is re-submitted for permanent sections.

B. The specimen consists of a 6 gm., 2.5 x 2.0 x 1.0 cm. ovary. The outer surfaces are smooth and glistening. It is sectioned. Its cut surfaces are unremarkable. The fallopian tube measures 3.0 cm. in length and 0.5 cm. in diameter throughout. There is a 1.0 cm. diameter smooth lined paratubal cyst present (inked blue). Its serosal surfaces are unremarkable. The cut surfaces are normal. Both the ovary and all of the fallopian tube are submitted.

C. Labeled appendix. Received is a S-shaped grossly intact vermiform appendix 9.3 x 0.8 cm. The serosa is pink-tan, glistening and reveals numerous congested vessels. A small mesoappendix is also present. Representative sections.

**MICROSCOPIC DESCRIPTION:
PERFORMED.**

FROZEN SECTION DIAGNOSIS:

A. FIBROSIS ONLY. NO EVIDENCE FOR ENDOMETRIOSIS.
Diagnosis given to Dr. _____ intra-operatively.

FINAL DIAGNOSIS:

A. PELVIS, SIDENALL, BIOPSY:
FIBROSIS.
NEGATIVE FOR ENDOMETRIOSIS.

Patient
Locati
Client:
PHYSICIA

PATHOLOGY

Patient

Patient

Sex: F DOB: 10/05/60 Age: 37 YRS

SURGICAL PATHOLOGY

Collection Date : 07/08/98

Accession: _____

FINAL DIAGNOSIS:

- B. RIGHT OVARY AND FALLOPIAN TUBE, SALPINGO-OOPHORECTOMY:
SEROUS ADHESIONS, OVARY.
BENIGN PERITUBAL CYST, FALLOPIAN TUBE (SEE COMMENT)
- C. APPENDIX, APPENDECTOMY:
NO PATHOLOGIC DIAGNOSIS.

COMMENT:

There is evidence of old hemorrhage within the benign peritubal cyst but it does not have features of endometriosis. In addition, one of the ovarian adhesions is associated with recent and past hemorrhage but endometriosis can not be documented (additional section examined).

07/10/98

(Electronic Signature)

Patient: _____
Location: _____
Client: _____
PHYSICIAN: _____

PATHOLOGY

Page 2
END OF REPORT

TOTAL P.03
TOTAL P.03



Study/Patent identity B351/518/0027

Sex, age, race: female, 13yr, Caucasian

Past history: cystectomy on L & R-ovaries (Mar98); migraine; recurrent pharyngitis.

Summary case history: **Surgery for R-abdominal pain associated with ovarian cyst. Acute appendicitis at pathology.**

The patient began treatment in this double-blind study on 12 June 1998.

She had a 3-year history of IBS. In March 1998 she had undergone surgery for bilateral ovarian cysts. She completed the study on 16Sep98. Four days previously, on 12Sep severe abdominal pains had appeared and she had presented at an emergency room two days later where a US scan showed the presence of a R-ovarian cyst. On 18Sep she underwent laparoscopy with R-ovarian cystectomy and appendectomy. Subsequent pathology concluded at an early acute appendicitis (no histology given for ovarian cyst).

Attachments: original serious adverse event report from investigator; history & physical admission report; operative report; pathology report.
(Hospital discharge notes requested but hospital requires newly-signed release request which may not be possible as family has moved and cannot be traced)

Accessory information (from case record form):

Study medication administration

Medication	Dosage (mg/d)	Dates
tegaserod	12	12Jun-16Sep98

Prior/Comedication

Medication (route)	ATC class	Dates
Paracetamol (oral)	anilides	Prior (1996)
Mg sulfate	Osmotic laxative	Prior (14-15Jun98)
EES	macrolide	29Jun-8Jul98
Mg citrate	osmotic laxative	20Jul98

All reported adverse events

Event	severity	Dates	Relationship*
Hot flushes	severe	22Jun98	possibly
Abdominal pain	mild	22Jun98	unrelated
Flatulence	moderate	22-26Jun98	unrelated
palpitations	moderate	22Jun98	possibly
Substernal muscle tenderness	mild	15-20Aug98	unrelated
R-lower abdominal pain	severe	12Sep98	unrelated
R-ovarian cyst	severe	12Sep98	unrelated

* relationship with study medication as assessed by investigator

SDZ HTF 919
Study Code: HTFB 351-E-00

ID 518 27
Center no. Subject no.

Subject's Initials

Date of report 23 SEP 98
day month year

SAE Report

SERIOUS ADVERSE EVENT REPORT

*See attached Instruction Sheet for information on completion of SAE Form. In addition, complete the ADVERSE EVENTS FORM

Date of birth 01 DEC 84 Weight 115 Height 63
day month year lbs inches

Sex Male Female Race Caucasian Black Asian/Oriental

Pregnant Yes No Not Applicable Other (specify): _____

Relevant medical history Ovarian cyst (L) (R) ovary - removed 03-98. Headaches + migraines - Recurrent since 1993. Recurrent sore throats since early childhood

ADVERSE EVENT specify as reported on AE form:

Clinical description (incl. diagnosis) (R) ovarian cyst which became symptomatic 12 SEP 98 with severe abdominal pains resulting in Emergency Room visit 14 SEP 98 and discharge. Resulting in inpatient surgery 17 SEP 98.

Reason for reporting
 Requires or prolongs hospitalization Cancer Life-threatening Death
 Persistently disabling or incapacitating Congenital anomaly Overdose
 Other (specify): _____

Start date 17 SEP 98 Start time unk End date 18 SEP 98 End time unk
 day month year 24 hr. clock day month year 24 hr. clock

Relevant findings (e.g. ECG, autopsy, lab data, Incl. copies of lab sheets)
ultrasound of 14 SEP 98 revealed (R) ovarian cyst

Therapeutic measures Hospitalization for removal

Course and outcome Laparoscopic removal of (R) ovarian cyst and appendix 18 SEP 98.

HTFB/351/0/518/27/USA
HTFB-351-518-027

SDZ HTF 919 Study Code: HTFB 351-E-00	ID <u>SIR</u> <u>27</u> <small>Center no. Subject no.</small> Subject's initials	SAE Report
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SERIOUS ADVERSE EVENT REPORT

In addition, please complete the 'ADVERSE EVENTS' form

STUDY MEDICATION

Daily dose _____ Start date of medication 22 JUN 98
day month year

Route of administration PO Time elapsed between last drug administration and onset of event _____

Dose reduction because of event No Not Applicable Yes → Date _____
day month year

Discontinuation because of event No Yes → Date _____
day month year

Code broken No Not Applicable Yes → Name of drug received _____

CONCOMITANT MEDICATION

Drug name	Indication	Daily dose at time of event	Route of administration	Start date	End date
Tylenol	Headaches	1 Tab	PO	1996	ongoing
Tylenol	Migraines	1 Tab	PO	1996	ongoing

ASSESSMENT OF CAUSALITY

Event causality Study indication Concomitant therapy Other, specify _____
 Coexistent medical condition Study medication

Relationship to study medication Not related Unlikely Possibly Probably Definitely

Justification of assessment given in Assessment of Causality (e.g. study indication, coexistent medical condition, concomitant therapy, study medication, other)

H/O ovarian cyst.
 Additional remarks none

Institution Gastroenterology Group of the Palm Beaches
 Investigator's name (please print) Steven Krumholz
 Investigator's signature [Signature]

HTFB/351/0/518/2/1/USA
 HTFB-351-5-027

HISTORY AND PHYSICAL

PATIENT NAME: _____

MR#: _____

ADMISSION DATE
PHYSICIAN: _____

DATE OF BIRTH:
December 1, 1984.

CHIEF COMPLAINT:
Right lower quadrant abdominal pain.

HISTORY OF PRESENT ILLNESS:
The patient is well known to me. In March she has bilateral ovarian cysts that required operation at _____. She had a rather impressive right-sided ovarian cyst. She recovered quite uneventfully from this procedure. She has been followed in my office. Approximately one month ago I obtained an ultrasound, which showed totally normal ovaries.

Last Monday, the patient began to have right lower quadrant pain and a repeat ultrasound now shows a 4.0 to 5.0 cm right ovarian cyst. Therefore she is now admitted to the hospital for diagnostic laparoscopy and management of this, to either take care of the cyst or to ensure that there is no ovarian torsion.

PAST MEDICAL HISTORY:
As above. She also has irritable bowel syndrome, for which she is on an experimental medication.

PAST SURGICAL HISTORY:
As above.

PHYSICAL EXAMINATION:
VITAL SIGNS: The child is afebrile.
CHEST: The lungs are clear.
HEART: The heart is regular.
ABDOMEN: She has a palpable fullness in the right lower quadrant. She is currently having her menses. The prior Pfannenstiel incision has healed well.

RECOMMENDATIONS:
I will admit her and perform a diagnostic laparoscopy and take care of this right ovarian cyst. Additionally, since she is having frequent ovarian cysts as well as inflammatory bowel, if everything

HISTORY AND PHYSICAL

PATIENT NAME
PHYSICIAN:

MR#:

goes well we will perform an incidental appendectomy, so that this way the picture will never be confused in the future.

AUTOMATIC AUTHENTICATION

DI 09/18/98 13:37
TI 09/19/98 13:09

CC:

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ST. MARY'S MEDICAL CENTER
WEST PALM BEACH, FLORIDA

OPERATIVE REPORT

PATIENT NAME: _____ MR#: _____

DATE OF OPERATION: _____

DATE OF BIRTH: 12/01/84

PREOPERATIVE DIAGNOSIS:
Right ovarian cyst.

POSTOPERATIVE DIAGNOSIS:
Right ovarian cyst.

OPERATIONS:

1. Diagnostic laparoscopy.
2. Laparoscopic lysis of adhesions.
3. Unroofing of right ovarian cyst.
4. Laparoscopic appendectomy.

SURGEON:

ANESTHESIA:
General endotracheal.

ESTIMATED BLOOD LOSS:
Minimal.

SPECIMEN SENT TO LABORATORY:
Removed appendix.

INDICATIONS FOR PROCEDURE:

The patient is a 13-year-old girl, well known to me. She had a prior bilateral ovarian cystectomy approximately six months ago. She was seen in my office and followed by ultrasounds which up until a month ago were normal. She presented last Monday with right lower quadrant pain. An ultrasound was obtained which showed a 4-5 cm right ovarian cyst. Therefore, she presents for diagnostic laparoscopy.

DESCRIPTION OF PROCEDURE:

After satisfactory induction of general endotracheal anesthesia, the abdomen was prepped with Betadine. She was given a gram of Ancef and oral gastric tube was placed by the anesthesiologist. A Foley catheter was placed. The abdomen was prepped with Betadine and draped in the usual manner.

OPERATIVE REPORT

PATIENT NAME: _____

NO: _____

The abdomen was entered using Hasson technique by placing a 12 mm trocar under direct vision. Upon entry into the abdominal cavity, intraperitoneal placement was confirmed and then the abdomen was insufflated to approximately 10 mmHg. At this point, inspection revealed some omental and bowel adhesions down in the low anterior abdominal wall. Two 5 mm ports were placed under direct vision at each end of her prior Pfannenstiel incision. The ports were placed under direct vision. Prior to placement, the wounds were infiltrated with 0.5% Marcaine with epinephrine. Prior to placement of the infraumbilical port, this was also infiltrated with 0.5% Marcaine. Using these two lower 5 mm ports as working ports, all of the adhesions were taken down using both blunt and sharp dissection. Eventually we were able to visualize the pelvis very well. The left tube and ovary was unremarkable. The uterus was engorged. The patient is currently having her menses. The right ovary had a 5 cm simple cyst. Bovis electrocautery was used to unroof this cyst. Thin serosanguineous fluid escaped. Hemostasis was good.

At this point, the attention then turned to the appendix. I did talk with the mother before hand that we would take the child's appendix out since these ovarian cysts seem to be a recurrent problem, as well as her having irritable bowel syndrome. The appendix was grasped near its mid portion and elevated up. The window was created at the base of the appendix in the mesoappendix. At this point, the camera was changed out. The 5 mm camera was placed in the left lower quadrant port. The stapling apparatus was placed in through the 12 mm infraumbilical port. The stapler was used to divide the appendix at its base with the cecum. A second reload was then used to divide the mesoappendix. The appendix was withdrawn up into the port and was removed through the port. At this point, the 10 mm camera was again changed out. The Nezhat suction irrigator was placed into the abdomen. All of the prior cyst fluid was irrigated out. The abdomen was allowed to desufflated to a pressure of about 5 and again was inspected. Hemostasis on the ovarian cyst wall was good. Hemostasis at the mesoappendix was good.

At this point, the trocars were removed under direct vision. The wounds all looked good. The pneumoperitoneum was allowed to escape and then the camera and 12 mm port were removed. The fascia of the 12 mm port site was closed with a figure-of-eight 2-0 Vicryl. The skin of all wounds was closed with 4-0 Vicryl buried subcuticular, followed then by Mestisol and Steri-Strips.

OPERATIVE REPORT

PATIENT NAME: _____

MRN: _____

The child tolerated the procedure well and was taken to the recovery room.

The operative findings, postoperative care, and the expected postoperative course were discussed with the mother.

AUTOMATIC AUTHENTICATION

D: 09/18/98 22:25
T: 09/21/98 15:24

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Patient Name:
Location:
Att Phys-Serv:
Submitting Phys:

- PEDIATRICS

DOB: 12/01/75
Completed:
Received:
Submitted:

CASE#:

SURGICAL PATHOLOGY

APPENDIX

CC:

Operation: Appendectomy
Pre-Op: Right Ovarian Cyst
Post-Op: Same

GROSS DESCRIPTION:

Received in formalin labeled "appendix" is a vermiform appendix measuring 7.0 cm in length and 0.5 cm in diameter. The appendix is light tan to pink and grossly congested with a few thin membranous adhesions. The attached adipose tissue is yellow lobulated and glistening. Sectioning reveals a patent lumen which is partially filled with a hard to pink bloody material. No discrete fecalith or perforation is noted. All tissue excluding adipose tissue is processed three blocks.

MICRO DIAGNOSIS:

EARLY ACUTE APPENDICITIS.

INFLAMMATORY CELLS, BACTERIA. LAMINA PROPRIA SHOWS LYMPHOID HYPERPLASIA. NO INFLAMMATION OF MUSCULAR WALL OR SEROSA IS SEEN.

Electronically Signed by:

SURGICAL Report
Duplicate

(Continued on next page)