coronary artery disorder (n=3)
diarrhea (n=3)
headache (n=3)
myocardial infarction (n=3)
skin carcinoma (n=3).

There were no further withdrawals for adverse events in patients receiving PL (cumulative total = 10) or OME (cumulative total – 19)[6]. No patient received RAN or FAM during the update reporting period.

IX. ASSESSMENT OF TESS

- In the North American GERD maintenance extension trial, AEs were reported in 93% of patients who received Aciphex™ (all doses combined). The proportion of pts. experiencing AEs by dose was 97% in the Aciphex™ 10 mg group, 90% in the Aciphex™ 20 mg group and in 96% of those receiving PL. The most common AEs (i.e. ≥5%) reported in the Aciphex™ combined group are listed in Table 4.

  - There was no apparent dose effect regarding the proportion of pts. experiencing AEs.

  - The following AEs – occurring at a frequency greater than 10% - were reported more frequently in the Aciphex™ combined group than in the PL group.

    abdominal pain
    diarrhea
    flatulence

  - Data displayed on sponsor's Table 6.9 (from which Table 4 was excerpted by the reviewer) indicate no meaningful increase in the incidence or nature of AEs reported in the extension trials since the filing of the NDA. When considering AEs experienced at an incidence greater than 10%, flu syndrome, surgical procedure, fever, diarrhea, and nausea were reported more frequently for the Aciphex™ combined group in the North American GERD Extension Studies compared with the North American GERD Maintenance Studies.

[6] Sponsor's NDA Section 6.4, ISS, vol. 249, p. 334

TABLE 4
NDA 20-973 SU

Number (%) of Patients with TESS Reported by at Least 1% of Patients in The Aciphex™-Combined – North American GERD Maintenance Trials

	NDA 20-973[a] Number and Percent of Patients				120-DAY UPDATE[b] Number and Percent of Patients			
	Aciphex™				Aciphex™			
	10	20	Combined	Placebo	10	20	Combined	Placebo
Total Number of Patients	165	163	328	169	69	93	162	27
Any TESS Adverse Event	138 (84%)	134 (82%)	272 (83%)	101 (60%)	67 (97.1%)	84 (90.3%)	151 (93.2%)	26 (96.3%)
Rhinitis	34 (21%)	28 (17%)	62 (19%)	16 (9%)	27 (39%)	27 (40%)	64 (40%)	10 (37%)
Diarrhea	37 (22%)	37 (23%)	74 (23%)	18 (11%)	31 (50%)	31 (33%)	62 (38%)	7 (26%)
Headache	33 (20%)	28 (17%)	61 (19%)	19 (11%)	22 (32%)	21 (23%)	43 (27%)	8 (30%)
Flu Syndrome	20 (12%)	22 (d13%)	42 (13%)	8 (5%)	18 (26%)	24 (26%)	42 (26%)	6 (22%)
Pharyngitis	26 (16%)	26 (16%)	52 (16%)	14 (8%)	17 (25%)	24 (26%)	41 (25%)	4 (15%)
Abdominal Pain	24 (15%)	19 (12%)	43 (13%)	5 (3%)	18 (26%)	18 (19%)	36 (22%)	3 (11%)
Surgical Procedure	14 (8%)	14 (9%)	28 (9%)	4 (2%)	13 (19%)	19 (20%)	32 (20%)	4 (15%)
Back Pain	18 (11%)	15 (9%)	33 (10%)	9 (5%)	14 (20%)	14 (15%)	28 (17%)	5 (19%)
Sinusitis	12 (7%)	17 (10%)	29 (9%)	7 (4%)	13 (19%)	13 (14%)	26 (16%)	3 (11%)
Pain	20 (12%)	11 (7%)	31 (9%)	5 (3%)	14 (20%)	10 (11%)	24 (15%)	3 (11%)
Dizziness	12 (2%)	6 (4%)	18 (5%)	2 (1%)	13 (19%)	6 (7%)	19 (12%)	2 (12%)
Accidental Injury	14 (8%)	13 (8%)	27 (8%)	3 (2%)	9 (13%)	10 (11%)	19 (12%)	2 (7%)
Asthenia	4 (2%)	10 (6%)	14 (4%)	9 (5%)	8 (12%)	9 (10%)	17 (11%)	2 (7%)
Vomiting	7 (4%)	15 (9%)	22 (7%)	11 (7%)	7 (10%)	11 (12%)	18 (11%)	3 (11%)
Insomnia	9 (5%)	13 (8%)	22 (7%)	7 (4%)	2 (3%)	2 (2%)	4 (3%)	0 (0%)
Infection	12 (7%)	4 (2%)	16 (5%)	4 (2%)	8 (12%)	10 (11%)	18 (11%)	3 (11%)
Flatulence	13 (8%)	11 (7%)	24 (7%)	8 (5%)	9 (13%)	8 (9%)	17 (11%)	0 (0%)
Cough Increased	6 (4%)	10 (6%)	16 (5%)	8 (5%)	7 (10%)	11 (12%)	18 (11%)	4 (15%)
Chest Pain	10 (6%)	7 (4%)	17 (5%)	2 (1%)	10 (15%)	6 (7%)	16 (10%)	2 (7%)
Myalgia	5 (3%)	10 (6%)	15 (5%)	1 (7%)	6 (9%)	8 (9%)	14 (9%)	0 (0%)
Fever	8 (5%)	10 (6%)	18 (5%)	5 (3%)	18 (26%)	24 (26%)	42 (26%)	6 (22%)
Bronchitis	7 (4%)	9 (6%)	16 (5%)	3 (2%)	5 (7%)	9 (10%)	14 (9%)	1 (4%)
Hypertension	4 (2%)	5 (3%)	9 (3%)	2 (1%)	5 (7%)	10 (11%)	15 (9%)	0 (0%)
Constipation	9 (5%)	9 (6%)	18 (5%)	3 (2%)	7 (10%)	6 (7%)	13 (8%)	2 (7%)
Anxiety	6 (4%)	6 (4%)	12 (4%)	2 (1%)	5 (7%)	7 (8%)	12 (7%)	1 (4%)
Dyspepsia	7 (4%)	3 (2%)	10 (3%)	13 (8%)	9 (13%)	2 (2%)	11 (7%)	3 (11%)
Gastrointestinal Disorder	5 (3%)	5 (3%)	10 (3%)	1 (1%)	7 (10%)	4 (4%)	11 (7%)	0 (0%)
Arthralgia	7 (4%)	3 (2%)	10 (3%)	5 (3%)	8 (12%)	4 (4%)	12 (7%)	3 (11%)
Rash	7 (4%)	6 (4%)	13 (4%)	2 (1%)	6 (9%)	4 (4%)	10 (6%)	1 (4%)
Neck Pain	6 (4%)	4 (2%)	10 (3%)	1 (1%)	5 (7%)	5 (5%)	10 (6%)	0 (0%)
Prostatic Disorder	4 (2%)	3 (2%)	7 (2%)	1 (1%)	4 (6%)	5 (5%)	9 (6%)	0 (0%)

a) Protocols include NRRK-EVEN and NRRK-ODD. Data Source: NDA 20-973, ISS 6-95
b) Data Source: Sponsor's Table 10A (Volume 2, Appendix 1, p. 13). Protocol includes 309.

- Similar to what was observed in the original GERD Maintenance trials in the NDA submission, the incidence of AEs was less in the European extension trial (Study #044-310) relative to the North American study. AEs were reported in 65% of patients who received Aciphex™ (all doses combined). The incidence of AEs by dose was 69% in the Aciphex™ 20-mg group, 62% in the Aciphex™ 10 mg group, and 58% in the OME group. The most common AEs (i.e., ≥5%) reported in the combined Aciphex™ group were:

  flu syndrome (11%)
  infection (10%)
  diarrhea (9%)
  surgical procedure (6%)
  abdominal pain, headache and nausea (5%)

  As was the case in the North American trial, no apparent dose effect was noted and the incidence of AEs reported in the Aciphex-treated patients was similar to that reported in the OME-treated patients. The incidence of AEs for the Aciphex™ combined group in European GERD Extension Studies was generally consistent with the European Maintenance Studies reported in the NDA.

- The proportion of patients experiencing TESS in the Aciphex™ combined group in the GERD Extension Studies conducted both in North America and Europe were generally comparable to those in the GERD Maintenance Studies. As illustrated in Table 5, when considering events occurring at a frequency greater than 5%, flu syndrome, diarrhea and rhinitis were reported more frequently in the Aciphex™ combined group in the GERD Extension studies than in the GERD Maintenance studies. Also included in this Table are 4 TESS that were reported by at least 5% of pts. in the combined GERD Maintenance CC and Extension S (North America and Europe) [120 Day SU but with 0 (0%) frequency in the NDA 20-973 report.

- AEs experienced by patients during maintenance therapy whether receiving RABE or PL, occurred in large part during the first year of therapy.

- Within each of the study phases (acute, maintenance, 1st year extension and 2nd year extension) the incidence of AEs was comparable between the Aciphex™ and PL groups (sponsor's Table 6.12). The percentages in the 3rd year extension consisted of relatively few patients having entered this phase by the data cutoff date.

- As was the case in the North American trials, the incidence of AEs in the European GERD Studies was greater in the GERD Maintenance Studies compared with the GERD Extension Studies. Again, most AEs occurred during the first year of Aciphex™ treatment.

  Study E3810-E033-311 (RABE 10 mg b.i.d. vs 20 mg OD vs OME 20 mg OD for 8 weeks in acute GERD trials) showed no considerable differences between RABE sodium (10 or 20 mg) and OME 20 mg with regard to AEs. No pattern of AEs emerged in any of the Tx groups.

A. Analysis of TESS by Severity (Table 6)

This Table summarizes the overall proportion of patients with mild, moderate or severe TESS for all GERD Maintenance and GERD Extension CCS in North America and Europe. The 120-Day SU showed that, regardless of TESS severity examined, there was no dose effect and RABE sodium-treated patients experienced TESSs which severity was similar to that of comparators (PL in the North American trials and OME in the European studies). The same conclusions were reached when analyzing the NDA TESS data by severity.

B. Analysis of TESS Possibly or Probably Related to Test Medication

Regardless of the geographic location the overall incidence of possibly or probably related AEs , **in the GERD maintenance extension studies**, was comparable between RABE sodium and PL in North America and RABE sodium and OME in Europe. As in the NDA, no dose effect was observed.

TABLE 5
NDA 20-973 SU

Proportion of Aciphex™ Treated Patients with TESS in the Combined GERD Maintenance Controlled Clinical and Extension Studies
(North America and Europe)
120 Day SU vs NDA 20-973

COSTART Term	Aciphex™ Combined	
	NDA 20-973[a] Number and Percent of Patients	120-Day Update[b] Number and Percent of Patients
Total Number of Patients	488	292
Any TESS Adverse Event	361 (74%)	236 (81%)
Flu syndrome	54 (11%)	55 (19%)
Diarrhea	84 (17%)	73 (25%)
Rhinitis	68 (14%)	67 (23%)
Hypertension	0 (0%)	20 (7%)
Migraine	0 (0%)	20 (7%)
Gastroenteritis	0 (0%)	14 (5%)
Anxiety	0 (0%)	13 (5%)

Excerpted from Sponsor's Table 6.11 of SU.
a) Data Source: NDA 20-973, ISS 6-80; Protocols include NRRK and NRRQ.
b) Data Source: Sponsor's Table 11 (Volume 2, Appendix 1, p. 36). Protocols include 309 and 310.

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TABLE 6
NDA 20-973 SU

Number (%) of Patients with TESS, According to Severity – Reported by At Least 1% of Patients in the Aciphex™ Combined Group GERD Maintenance Controlled Clinical Studies and Extension Studies

I. North America

COSTART Term	NDA[a]				120-Day Safety Update[b]			
	Aciphex™			Placebo	Aciphex™			Placebo
	10 mg	20 mg	Combined		10 mg	20 mg	Combined	
Total No. of Pts.	165	163	328	169	69	93	162	27
Any MILD TESS AE	115 (70%)	110 (67%)	225 (69%)	74 (44%)	61 (88%)	73 (79%)	134 (83%)	24 (89%)
Any MODERATE TESS AE	93 (56%)	95 (58%)	188 (57%)	54 (32%)	57 (83%)	69 (74%)	126 (78%)	19 (70%)
Any SEVERE TESS AE	33 (20%)	33 (20%)	66 (20%)	24 (14%)	21 (30%)	26 (28%)	47 (29%)	8 (30%)

II. Europe

COSTART Term	NDA[a]				120-Day Safety Update[b]			
	Aciphex™			Omeprazole				Omeprazole
	10 mg	20 mg	Combined		10 mg	20 mg	Combined	
Total No. of Pts.	82	78	160	83	66	64	130	64
Any MILD TESS AE	32 (39%)	39 (50%)	71 (44%)	29 (35%)	35 (53%)	40 (63%)	75 (58%)	31 (49%)
Any MODERATE TESS AE	15 (18%)	13 (17%)	28 (18%)	18 (22%)	15 (23%)	14 (22%)	29 (22%)	17 (27%)
Any SEVERE TESS AE	6 (7%)	6 (8%)	12 (8%)	7 (8%)	5 (8%)	6 (9%)	11 (9%)	5 (8%)

North America

MILD
a) Data Source: ISS Table 6JJ NDA 20-973-(NRRK-even and NRRK-odd)
c) Data Source: Sponsor's Table 26 (Volume 2, Appendix 1, p. 241). Protocol includes 309.

MODERATE
a) Data Source: ISS Table 6KK; NDA 20-973 – (NRRK-even and NRRK-odd)
b) Data Source: Sponsor's Table 22 (Volume 2, Appendix 1, p. 177). Protocol includes 309.

SEVERE
a) Data Source: ISS Table 6LL NDA 20-973 – (NRRK-even and NRRK-odd)
b) Data Source: Sponsor's Table 18 (Volume 2, Appendix 1, p. 150). Protocol includes 309.

Europe

MILD
a) Data Source: ISS Table 6MM NDA 20-973 – (Protocol NRRQ)
b) Data Source: Sponsor's Table 27 (Volume 2, Appendix 1, p. 253). Protocol includes 310.

MODERATE
a) Data Source: ISS Table 6NN NDA 20-973 – (Protocol NRRQ)
b) Data Source: Sponsor's Table 23 (Volume 2, Appendix 1, p. 186). Protocol includes 310.

SEVERE
a) Data Source: ISS Table 600 NDA 20-973 – (Protocol NRRQ)
b) Data Source: Sponsor's Table 19 (Volume 2, Appendix 1, p. 154). Protocol includes 310.

Patients with occurrences in more than one COSTART term are counted only once in the Any TESS AE total.

C. AEs of Particular Interest

1. Blood Dyscracias

a) **Thrombocytopenia**

During the Aciphex™ clinical development program there were no serious reports or withdrawals from therapy for thrombocytopenia in any Tx group.[7] Since the initiation of marketing of Pariet in Japan, there have been 10 reports of thrombocytopenia in Pariet-treated Japanese patients (from October 14, 1997 through August 31, 1998). These events were previously summarized in Section VII. A. of this review. There was no apparent dose relationship, and no clear age or gender relationships in these 10 reports. Six patients were F (ages 27-80 y) and 4 were M (ages 51-73 y). Time to onset of thrombocytopenia ranged from 6 to 70 days. Two of the patients developed symptomatology associated with the condition (Aris nos. –118, and –077) and the remainder were diagnosed from laboratory tests. Recovery was reported for 6 of the patients, with time to recovery ranging from 5 to 44 days. Two were reported as being improved (within 7-10 days), but complete recovery was not reported (Aris nos. –058 and –118). All 10 were receiving at least one concomitant therapy in addition to Aciphex™. Maalox® was the most frequent additional medication in this group (n=4), followed by FAM, rebamipide, and polaprezine (3 patients each). Nine of the ten were considered to be related to Aciphex™ by either the reporter, the sponsor, or both,at the time of pharmacovigilance reporting [this reviewer assessed 4 of the 9 cases to be related to test medication].

In conclusion, at the present time, 4[8] of the 10 reports of thrombocytopenia could be reasonably attributed to Aciphex™ exposure, which now exceeds 6 million patient days. It is recommended to carefully monitor subsequent events of thrombocytopenia and cumulative incidence.

b) **Leukopenia and Pancytopenia**

During the Aciphex™ clinical development program, there were no serious reports or withdrawals from therapy for leukopenia in Aciphex™-treated subjects.[9]

Since the initiation of marketing of Pariet in Japan, there have been 3 reports of leukopenia and one of pancytopenia in Pariet-treated Japanese patients through August 31, 1999. These events, which were previously summarized in Section VII. A. of this review, were described in sponsor's Table 6.32. All were considered to be related to Tx with Aciphex™ by both the reporting physician and the sponsor at the time of pharmacovigilance reporting. This reviewer agreed with this assessment of causality. Although details of at least one of the cases are scanty and there were potential confounders in others, this reviewer is of the opinion that,

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[7] During acute controlled trials in North America and Europe, 2 Aciphex™-treated subjects (<1%, n-981) reported treatment-emergent abnormal platelet counts, and none was reported during the GERD maintenance trials.

[8] Aris Nos. J-1RS-00018 (27 y old F); -000037 (80 y old F); -000084 (70 y old M) and –000082 (60 y old F); all Japanese patients.

[9] 1 FAM patient was reported to have withdrawn from a trial for leukopenia (57-year old Japanese female, patient no. 14-2 in study no. J-013). Less than 1% of Aciphex™-treated patients in acute clinical trials and GERD maintenance studies in North America and Europe experienced treatment-emergent low white cell counts.

conservatively, the terms leukopenia and pancytopenia should be incorporated in the labeling as rare events in association with the drug. In addition, careful monitoring of blood dyscracias should continue, with particular emphasis on thrombocytopenia, leukopenia and pancytopenia.

2. Cardiovascular Events

a) **Sudden Death**

There have been two sudden deaths during Tx with Aciphex™ [E3810-E044-310, Pt. 124/5002, a 74y old M, and J-IRS-000049 Pt. S-H, a 45y old M]. The first, which was reported in the ISS, occurred in Poland in March 1997, occurred after 459 days of exposure to 20 mg of the drug. The second was reported in April 1998 through post-marketing safety surveillance in Japan. Both subjects died while sleeping.The events leading to death in the second patient were discussed in Section VI. of this review. This reviewer concluded that RABE sodium cannot be completely exonerated as a possible cause of death in this patient and that – conservatively – this information should be included in the labeling, under rare events, with an appropriate disclaimer. This is because, at present, there are no convincing findings that the drug is a direct or indirect cause of sudden death.

b) **Cardiac Dysrhythmia**

Table 7 presents a cumulative list of all reported cases of arrhythmia, sorted by dose and type of arrhythmia. A detailed evaluation of these cases resulted in the conclusions on relationship summarized in the last column of this Table. This reviewer agrees with the sponsor that, these data, when considered together, suggest that treatment with Aciphex™ is neither directly nor indirectly associated with the development of those varied cardiac arrhythmias. Nonetheless, the drug can not be completely exonerated as being associated with the rare occurrence of some arrhythmias (including the one case of sudden death) and this information should be included in the labeling.

c) **MI, Chest Pain and Angina**

This issue originated some concern during the review of safety for the DU indication and was therefore addressed in utmost detail in the review of the ISS (December__, 1998). Some findings are recapitulated here and new information (if any) is considered as part of an overall assessment of the subject matter.

TABLE 7
NDA 20-973 SU

List of Patients Who Experienced Cardiac Dysrhythmias During Treatment With Aciphex™ Through August 31, 1998

Study no. or ARIS no. (Source Data)	Pt. ID	Type of Dysrhythmia (Outcome) Duration of Exposure (days)[a]	Related?		
			RP or PI	SP	Reviewer
I. Total Daily Dose of Aciphex™: 10 mg					
E3810-A001-309 (ISS)	030/19205 (45 F)	Bradycardia (Unknown) (550)	No relationship	No relationship	NO
H4M-MC-NRRQ (ISS)	124/4006[b] (43 M)	IHD with bradycardia (Unknown) (9)	No relationship	No relationship	NO
J-IRS-000069 (A1)	[redacted] (37 F)	Complete heart block (Pacemaker implanted)	Possibly	Unlikely	NO
H4M-MC-NRRK (ISS)	067/9249[b] (64 M)	Multiple atrial & ventricular arrhythmias (Recovered) (248)	Possibly	Possibly	POSS
II. T otal Daily Dose of Aciphex™: 20 mg					
J-IRS-000074 (A1)	[redacted] (49 M)	Bradycardia (Recovered) (9)	Likely	Possible	POSS
E3810-A001-309 (ISS)	060/19414 (75 F)	3rd degree AV block and bradycardia (Death due to cardiopulmonary arrest) (885)	No relationship	No relationship	NO
J-IRS-000036 (A1)	[redacted] (81 F)	Ventricular arrhythmia and QT prolongation (Recovered) (18)	Unlikely	Unlikely	NO
[redacted]	[redacted]	[redacted]			
H4MC-NRRK (ISS)	041/9287 (79 F)	Multifocal atrial tachycardia (Unknown) (105)	No relationship	No relationship	NO
J-IRS-000049 (A1)	[redacted] (45 M)	Suspected cardiac arrhythmia[c] (Death) (27)	Unlikely	Possibly	POSS
H4-MC-NRRD (ISS)	022/5148[b] (53 M)	Increased & irregular heartbeats (Recovered) (4)	No relationship	Remotely	NO

Source Data: A1=Patient narratives, sponsor's Volume 4, Appendix 2. ISS=Patient narratives, ISS (March 15, 1998)
RP = Reporting physician. PL = Principal investigator, SP = Sponsor, IHD = Ischemic heart disease.

a) At the time of onset of the event.
b) Patient withdrawn from the clinical trial for this event.
c) Event recorded in database as "sudden death".

- The ISS (March 15, 1998) reported MI in 10 patients through February 3, 1998. One occurred during screening, and 9 were reported in patients who received Aciphex™. One of these patients (pt. no. 122/4001 in study no. NRRQ) had two MIs. Although the investigator attributed MI as the cause of the death of patient no. 124/5002 in study no. E810-E044-310 (discussed above), there was no Hx of chest pain or any other corroborating information supporting a diagnosis of MI. Therefore, this event was considered to be a sudden death rather than secondary to MI. It needs to be noted, however, that unless MI was r/o by autopsy, sudden death can still be due to MI. There were no reports of MI in patients who received PL or comparators. As indicated in the ISS review, this imbalance was considered to be a statistical fluctuation, since appraisal of these cases showed no apparent relationship to Aciphex™ treatment.

- It is worth noting that, as of August 31, 1998, there have been no further reports of MI in clinical trials in North America or Europe, or during post-marketing safety surveillance in Japan.

- In addition to the 32 Aciphex™-treated patients who experienced chest pain and 2 who reported angina pectoris in clinical studies through February 3, 1998, there were 3 additional SAEs of chest pain in Aciphex™-treated GERD patients in L-T clinical studies from February 4, 1998 through August 31, 1998. One of these cases led to the D/C of Aciphex™, but was considered to be a manifestation of GERD-associated gastrointestinal pain (pt. no. 006/19708 in study no. E3810-A001-301-1). None was considered to be related to Aciphex™ by either the investigator or the sponsor.

From the above, the imbalanced report of MIs between RABE sodium and comparators in the NDA can be considered a statistical fluctuation.

3. Hepatic Dysfunction

As pointed out during the review of the ISS, there have been sporadic reports of hepatitis, elevated liver enzymes, jaundice and hepatic encephalopathy during the Aciphex™ clinical development program.[10] Events related to these categories are further discussed below.

a) **Hepatic Encephalopathy**

The ISS reported that 2 Aciphex™-treated patients with pre-existing liver disease developed hepatic encephalopathy. One patient consented to rechallenge in June 1998. A detailed description of this rechallenge, done in consultation with the agency, was included in the SU. The negative rechallenge provided no evidence that daily dosing with 20 mg Aciphex™ for 7 days caused worsening of this patient's #2005 (BED)] encephalopathy. A sponsor's consultant arrived at a similar conclusion. Additionally, in the Japanese post-marketing surveillance program,there was one report of coma and hyperammonemia in a Aciphex™-treated patient [Aris No. J-1RS-000078] with pre-existing hepatic dysfunction. Although not described by the

[10] It is of interest to note that hepatic dysfunction ranging from minor elevations of liver enzymes to fulminant liver failure has been reported during the use of the PPI omeprazole (ref. PDR).

reporter as "hepatic encephalopathy" this event is mentioned here because it represents a case of a severe neurological manifestation of hepatic dysfunction in a patient with pre-existing liver disease. This event was possibly related to Aciphex™.

b) **Hepatitis, Jaundice, and Abnormal Liver Function Tests**

Two Aciphex™-treated patients (0.1%, n=3556) and no comparator- or placebo-treated patients experienced a SAE of hepatitis; one of these led to the withdrawal of Aciphex™ therapy, and the second was an acute case of hepatitis A. One additional Aciphex™-treated patient reported liver damage due to chronic alcoholic liver disease. There were no serious reports or withdrawals for jaundice in any treatment group. Two Aciphex™-treated (0.1%), 1 OME-treated (0.2%, n=553), and 3 FAM-treated patients (1.0%, n=293) were withdrawn from studies for elevated liver enzymes.

It is noted that from February 4, 1998, through August 31, 1998, there were no further serious reports or discontinuations for hepatitis, jaundice, or abnormal liver function tests in ongoing clinical trials in North America or Europe.

The incidence of post-marketing reports of hepatic dysfunction has also been low. Since the initiation of marketing of Pariet in Japan, there have been four reports of abnormal LFTs and one report of jaundice during over 6 million patient-days of exposure to Pariet (from October 14, 1997 through August 31, 1998). These events were each considered to be related to Aciphex™. On the other hand, one patient with documented pre-existing liver dysfunction experienced no exacerbation of his liver disorder while receiving Aciphex™. Patient no. 063/19437 in study no. E3810-A001-309 (42-year-old Caucasian male), entered the trial with a 10-y Hx of hypertransaminasemia. During his approximately 2-1/2 y course of treatment with 20 mg Aciphex™ daily, the following laboratory values were reported.

4. Overdose Associated with Disorientation and Delirium

Ca. 3 weeks prior to the event, this 75-y-old Japanese M with Hx of mild senile memory loss, hepatic cancer and cirrhosis, was noted to have abnormal LFTs, and ca. one year prior to the event, he had a Hx of elevated ammonia level and indocyanine green test. The patient inadvertently took 30 mg of Aciphen™ rather than 10 mg and became confused. After stopping Aciphex™, his confusion started to resolve. He was again given Aciphex™ (10 mg) and again became confused. The MTL interprets this as a positive rechallenge. The investigator considered the confusion to be possibly related to Aciphex™. This patient's confusion could have been secondary to drug overdose exacerbating or due to his underlying senile memory loss. The sponsor believes that the contribution of his underlying liver disease to his confusion remains unknown.

Hepatic Profile for Patient No. 063/1943 in Study No. E3810-A001-309

Date	AP (15-110 U/L)	ALT (SGPT) (0-48 U/L)	AST (SGOT) (0-41 U/L)	Total BIL (0.3-1.3 mg/dL)	GGT (0-64 U/L)
Study Drug: Ranitidine 600 mg daily, May 2, 1995 – May 29, 1995					
May 2, 1995 (pre-ranitidine)	115 H	67 H	40	0.5	227 H
May 30, 1995 (pre-Aciphex™)	112 H	67 H	28	0.8	251 H
Study Drug: Aciphex™ 20 mg daily, May 31, 1995 – through at least Nov. 1997					
Sep. 15, 1995	82	30	16	0.7	130 H
Dec. 11, 1995	62	15	12	0.7	65 H
May 24, 1996	69	37	15	0.9	151 H
Aug. 22, 1996	103	61 H	32	0.5	251 H
Nov. 26, 1996	106	42	18	0.6	234 H
May 20, 1997	144 H	30	18	0.5	199 H
Approx. No. 1997	86	38	23	0.6	136 H
Source Data: Clinical databases for studies NRRJ, NRRK, 309 and 309-1.					

5. Hypersensitivity Reactions

There was a very low incidence of hypersensitivity reactions which were considered to be related to the administration of Aciphex™.

a) **Skin Hypersensitivity/Interstitial Pneumonia**

During the Aciphex™ clinical development program, through February 3, 1998, there were six reported discontinuations of Aciphex™ therapy (n=3556; 0.2%) for AEs reflective of skin hypersensitivity (rash, eczema, and allergic reaction) in studies in North America, Europe, and Japan. Two occurred in females aged 41 and 76 years, and four occurred in males aged 40-58 years. Aciphex™ doses were 10 mg (n=1), 20 mg (n=4), and 40 mg (n=1). Time to onset of these events ranged from 1 to 92 days, and recovery was reported for 3 of the 6 within 1-17 days. Incidences of similar types of AEs for PL and the comparators RAN, OME, and FAM were (respectively) 0.2% (n=521), 0% (n=537), 0.5% (n=553, and 0.3% (n=293)[11]. There were no further discontinuations for rash in Aciphex™-treated patients in ongoing clinical trials from February 4 through August 31, 1998.

- During post-marketing safety surveillance in Japan, there was one report of interstitial pneumonia along with hepatic enzyme elevations which was considered to be a possible drug hypersensitivity reaction (J-1RS-000062).

- During the first six months of commercial exposure to Aciphex™ in Japan (over 6 million patient-days), there was also a low incidence of serious spontaneous reports of skin hypersensitivity reactions.

[11] Reference: ISS, section 6.4, NDA vol. 249, p. 334-355.

6. **Increased TSH**[12]

Patient no. 037/19255 in study no. E3810-A001-309 developed an elevated TSH value after 11 months of Aciphex™ Tx. At BL her T_3 uptake was 24.3% (normal 22.0-35.0%) and ranged from 21% (L) to 22.8% during Aciphex™ treatment. Her lowest T_3 uptake value (21%) occurred in association with her highest TSH value of 11.9 mIU/mL (normal 0.4-5.5 mIU/ml). However, her T_4 and free T_4 index remained WNL throughout the study, and at no time was her thyroid palpably enlarged. The persistenly elevated TSH led to the withdrawal of the patient from the study. Three months after discontinuation of Aciphex™ therapy her TSH was reported to be WNL. This patient's TSH elevation was possibly related to Aciphex™ treatment.

7. **Gastric Carcinoma**

To date, there have been no cases of gastric carcinoma reported in clinical studies or through post-marketing safety surveillance.

D. Post-Market Surveillance

The sponsor notes that the International Birthdate for Aciphex™ ("Pariet" in Japan and Europe) was set in accordance with its first marketing authorization in Japan on October 14, 1997. A report summarizing the safety data received by Eisai Corporate Drug Safety from worldwide sources between October 14, 1997 and April 13, 1998 is contained in sponsor's Appendix 5. During the time period covered by this report, there were no changes in the medical texts (labeling) proposed by Eisai or the regulatory authorities for safety reasons and there have been no applications instituted by Eisai or the authorities for withdrawal of approval. There have been no restrictions on product distribution, no changes on target population or indication and no formulation changes.

The report encompases over 4,300 patients (equivalent to 159,000 patient day exposures) in clinical trial programs. On the basis of the once-daily dosing for the product, the global Aciphen™ experience exceeds 6 million patient days.

All serious events contained in this report were summarized under sponsor's section 6.2 of the SU document.

E. Publications

Sponsor's Appendix 3 contained a total of nine (9) publications which have been published since the cut-off date for the NDA.[13]

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[12] In animal studies, increased thyroid weights and hypertrophy of the thyroid were found in more than one animal species.

[13] Four of these publications are non-clinical pharmacology reports, three involve clinical trials which have already been reported in the NDA and the remaining two involve a guest commentary and a descriptive profile of Aciphex™.