EXECUTIVE SUMMARY

SUMMARY REVIEW OF OCTOBER 14, 1998 SAFETY UPDATE

The safety information included in this SU report covers the period between October 31, 1997 (the cut-off date for information included in the ISS) and May 22, 1998 (the cut-off date for safety information that was to be included in the periodic SU), except for SAEs and premature discontinuations due to AEs. The cut-off date for inclusions of these AEs into this SU report was August 31, 1998. The document reviewed here was submitted to the Agency on October 21, 1998. In the main, this submission presents additional safety data from ongoing GERD maintenance extension studies, safety data from all company-sponsored clinical trials initiated after the cut-off date for the NDA, post-marketing information from Japan and a very detailed reassessment of the long-term gastric biopsy data presented in the NDA. This re-analysis was carried out by Dr. Jerry Gardner, a recognized clinical expert in the field.

The database included **546** RABE-treated additional patients treated with RABE sodium. This number is <25% of the number of subjects (**3556** patients/volunteers) presented in the NDA who participated in the completed clinical trials and who were exposed to one or more doses of RABE in the clinical trials conducted in North America, Europe and Japan. Therefore, integration of the new information presented in this periodic SU report with the safety data presented in the NDA was not performed.

This supplementary information lends additional support to the conclusion that rabeprazole is safe. Incidences of withdrawals [due to AEs] under RABE were not different from those with placebo or a comparator. With regards to death or serious ("significant") adverse events, in no instance can these events can be attributed to the test medication (whether rabeprazole, placebo or an active comparator. Nonetheless, a case of sudden death in a relatively young person with no reported history of cardiovascular disorder and no apparent confounding medication and occurring in temporal association with the drug, should – conservatively – be included in the labeling.

The most frequent symptomatic adverse effects associated with rabeprazole were diarrhea and headache and this adverse event profile is similar to that seen with approved PPIs (omeprazole and lansoprazole). There was no meaningful increase in the incidence or nature of AEs reported in the extension trials since the NDA was filed. Assessment of the data on overall incidence of AEs noted in both the ISS and SU reports reveals a variety of annoying symptoms but these manifestations were not clearly related to rabeprazole. Again, from the post-marketing report in Japan, some rare occurrence of AEs that were considered to be possibly/probably related to the drug should be incorporated in the labeling. These included blood dyscracias, hepatic dysfunction, cardiovascular events and possible hypersensitivity reactions. No findings of particular concern were observed when evaluation was carried out of cardiovascular events, hepatic dysfunction, increased TSH and other clinical laboratory evaluations.

Also included in this review is a very detailed appraisal of the gastric biopsy data following long-term administration of the drug, presented in the NDA. Results from the extension studies of NRRK and NRRQ offered the opportunity to examine gastric mucosal pathology in patients treated for up to 5 years with rabeprazole or omeprazole. In some evaluations, the role of *H. pylori* infection was assessed. Not all findings previously reported with omeprazole were reproduced in the current studies. It is, however, concluded that nearly all pathologic changes, except for ECL cell hyperplasia, occurred in those patients with histologic evidence of *H. Pylori* infection. In most (but not all) studies, there was a dose response (20 mg > pathologic changes than 10 mg rabeprazole). As previously recommended, these observations should be included in the labeling.

Data from this SU confirm the conclusion stated in the review of the ISS report: rabeprazole is a safe and well-tolerated proton pump inhibitor. This appraisal has not revealed any disturbing findings or trends. The safety pattern – including that of cardiovascular events - is generally reassuring and suggests that clinically important drug-induced conditions are not being missed. This reviewer's recommendations to incorporate certain terms (AEs) in the labeling are not intended to raise concerns. These recommendations are justified on the basis of an anticipated, prolonged use of the drug and the rather limited information on the effects of long-term administration of rabeprazole to humans. However, borrowing from existing experience with omeprazole and lansoprazole, the two approved PPIs, no serious safety concerns are to be expected.

TABLE OF CONTENTS

I. SCORE OF MATERIAL REVIEWED

In NDA 20-973 (submitted March 31, 1998) data were presented in support of the safety and effectiveness of ACIPHEX™ (Rabeprazole) for five acid-related indications. Safety data for the individual indications were reviewed by Drs. Senior, Prizont and Gallo-Torres. The Integrated Summary of Safety, submitted as part of the initial NDA, was reviewed by Dr. Hugo Gallo-Torres (December , 1998). The safety information included in this SU report covers the period between October 31, 1997 (the cut-off date for information included in the ISS) and May 22, 1998 (the cut-off date for safety information that was to be included in the periodic SU), except for SAEs and premature discontinuations due to AEs. The cut-off date for inclusion of these AEs into this SU report was August 31, 1998. In the main, this submission presents additional safety data from ongoing GERD maintenance extension studies and these data are compared to information previously included in the NDA. In addition, a clinical study report for Study E3810-E033-311[1] is provided in sponsor's Appendix 13 of this amendment. But this study will not be reviewed for efficacy since, according to the sponsor, it provides no significant new efficacy information already presented in the original NDA. However, the safety data from this trial have been summarized in this SU. Also included in this SU is a sponsor's proposed modification of the "Adverse Reactions" Section of the product package insert to provide a more concise display of AEs for product labeling that was provided in the original NDA. Finally, the gastric biopsy data presented in the NDA have been further analyzed by Dr. Jerry Gardner, a recognized clinical expert in the field. The sponsor believes that these additional analyses provide a more complete clinical interpretation of the gastric biopsy data. It is noted that the overall conclusions regarding the safety of ACIPHEX™ (rabeprazole sodium) have not changed.

II. ADDITIONAL SAFETY DATABASE

Of the 69 clinical studies summarized in the NDA, several were ongoing at the time of the submission.[2] Since final reports are not available for the GERD Maintenance extension trials (studies 309 and 310), data analyses from these studies were performed from an interim database (data lock May 22, 1998). Data from the acute GERD trial (study 311) was extracted from a clinical study report. Data from the GAHS and ZES trial (study 501) have been compiled from CRFs for the 11 enrolled patients.

- Five other trials were initiated since the data cut-off for the NDA.

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[1] This active comparator trial, which was conducted in France, compares the efficacy and safety of RABE sodium 20 mg once daily vs RABE sodium 10 mg twice daily vs OME 20 mg once daily in the treatment of erosive or ulcerative GERD.

[2]

- 1 trial was an acute study conducted in Europe (E3810-E-033-311) for the Tx of patients with erosive or ulcerative GERD.
- 2 other trials (E3810-A001-309 and E3810-E044-310) were 2-year extension studies of the U.S. (NRRK) and European (NRRQ) GERD maintenance studies, respectively. These extension trials have been amended to extend the length of treatment to obtain up to five years of long-term therapy.
- Studies 309 and 309-1 had the same CRF (designed for two-year period); for presentation in this periodic SU, data was split-up into first and second year of the extension period.
- The remaining trial which is still ongoing (E3810-A001-501) is evaluating the safety and effectiveness of Aciphex™ for the Tx of patients with ZES or idiopathic gastric acid hypersecretion (GAHS).

- 1 of these trials (E3810-E033-116) is a European study evaluating esophageal acid exposure following one week of Tx with various doses of Aciphex™.

- 2 ongoing trials in Japan have also been initiated since the cut-off date for the NDA. Protocol PT001R00 is a study in healthy adult males in which the effect of single and seven consecutive doses of 10 mg ACIPHEX™ (Pariet™ / rabeprazole sodium) on gastric acid secretion is being assessed. (Pariet™ is the trade name used for rabeprazole sodium in Japan and Europe.) A second Japanese study (Protocol PT001S) is a retrospective survey for the purpose of checking the necessity of conducting special studies in a defined population or additional post-marketing clinical studies. No protocol number was initially assigned to this survey. As of the cut-off date for this periodic SU report, no databases were available to analyze the safety information for the two Japanese clinical trials. However, serious adverse events and/or D/C due to AEs have been presented in this periodic SU report.

- The fourth trial (E3810-A001-118) which was initiated and completed after the NDA cut-off date, was a single dose, 4-way cross-over, bioequivalence study in normal volunteers conducted in the US. A full clinical report for the 118 study was submitted to the FDA on June 30, 1998, and the safety data from that trial have been included in this SU report.

- The fifth trial is a study in Taiwan (E3810-S886-301) comparing RABE to CIM in the Tx of active GU. Limited data were available as of the cut-off data for date.

This periodic SU report contains the following new safety information:

(1) Safety data from the 10 mg bioequivalency study (E3810-A001-118)

(2) The International Periodic Safety Report for Pariet™ (RABE sodium) covering the period from October 14, 1997 (date of first approval worldwide) to April 13, 1998

(3) Safety data from Subject BED from Study E3810-A001-108 who, had hepatic dysfunction and was re-challenged with RABE

(4) A full clinical trial report for Study E3810-E044-311

(5) New safety data from the following ongoing studies: Studies E3810-A001-309, E2810-E044-310 and E3810-A001-501, which were not presented in the NDA

(6) Safety data from all company-sponsored clinical studies initiated after the cut-off date for the NDA

(7) Safety data from a literature search covering the period between October 31, 1997 and May 22, 1998

(8) All AEs reported to the FDA from October 31, 1997 to May 22, 1998, from clinical trials and post-marketing surveillance data

(9) Current package inserts from Japan (translated into English) and the U.K.

(10) New non-clinical toxicity data and

(11) Subject narratives and corresponding CRFs for each subject who died during a clinical study or who did not complete a clinical trial because of an AE.

In addition, a revised package insert for the U.S. in both hard copy and diskette (MS Word 97), and a re-analysis of the biopsy data from Studies NRRK (even) and NRRK (odd), and NRRQ, were included.

Of note, the number of new subjects exposed to Aciphex™ in all new or ongoing clinical trials since the October 31, 1997 cut-off date for the NDA is <25% of the number of subjects presented in the NDA. Therefore, no formal integration of the new information presented in this periodic SU report with the safety data presented in the NDA was performed. Finally, any new significant changes or findings, including any new AEs, are tabulated and identified in the SU document. Also, it is worth noting that this SU review is structurally similar to the review of the ISS (H. Gallo-Torres, December 22, 1998).

- Demographic characteristics for the GERD extension trials in North America and Europe were summarized by treatment group in sponsor's Table 4.1. The study population consisted of 48% to 68% M and 32% to 52% F patients across the Tx groups. The majority of patients were Caucasian (89% to 95.3%) in the four Tx groups; the remaining patients belonged to African descent and other races. There were no patients of African descent in the OME group in the European extension trials. The mean age ranged between 53.7 y and 57.4 y across the study groups.

  The demographic characteristics of the SU population were similar to the NDA population, with the exception of the proportions of M and F in the PL groups. There were ca. equivalent numbers of M and F patients in the extension trials, whereas M represented 62% of the patients in the NDA GERD Maintenance trials.

  Demographic characteristics were presented in sponsor's Table 4.2, and were similar between the North American and European patient populations and were consistent with the populations presented in the NDA.

III. GENERALITIES

When searching for clues as to what to look for or what to expect in terms of AEs with RABE, it is important to note that this compound is a proton pump inhibitor. Two PPIs are now available: omeprazole (OME; PRILOSEC®, Astra-Merck) and lansoprazole (LANSO, PREVACID®, TAP Pharmaceuticals). These (as well as RABE) are substituted benzimidazoles that suppress gastric acid secretion by specific inhibition of the H^+/K^+ATPase enzyme system at the secretory surface of the gastric parietal cell. PPIs block the final step of acid production. Animal studies indicate that after rapid disappearance from plasma, the PPIs can be found in the gastric mucosa for a day or more. Therefore, it is not surprising that in humans, duration of acid secretion inhibition after administration of PPIs is up to 72h. Additional important preclinical findings with PPIs are dose-related significant increases in gastric carcinoid tumors and ECL hyperplasia, shown in 24-month carcinogenicity studies in rats. Although these findings originated much concern during the review of the OME NDA 10 years ago (Hugo E. Gallo-Torres review of NDA 19-810, 1989) they are of lesser concern now because they are thought to result from the profound pharmacodynamic effect of these compounds. The mechanism of carcinoid production has not been completely elucidated but involves hypergastrinemia. It may also involve trophic peptides/prostaglandins, etc. Indeed, carcinoid tumors have also been observed in rats subjected to fundectomy or very high doses of H_2-receptor antagonists. In humans, long-term administration of PPIs has been associated with increased gastric atrophy. Although there may be an association with intestinal metaplasia I (not a pre-malignant condition) it has been hypothesized that there would be no progression to pre-malignant states (intestinal metaplasia III), unless there is co-existence of *H. Pylori* infection. In summary, in humans, the incidence of ECL cell hyperplasia increases with time but no case of ECL cell carcinoids, dysplasia or neoplasia has been found in patients treated with PPIs, long-term. Nonetheless, one important corollary from these considerations is that long-term administration of PPIs continues to require a lengthy follow-up with gastric mucosa biopsy. RABE is not an exception to this precautionary rule.

In controlled clinical trials, the AEs more frequently seen with PPIs include headache and those related to the underlying gastrointestinal tract conditions. These compounds are perceived as very safe, especially for short-term administration. Although PPIs are metabolized via the cytochrome P_{450} system and dozens of drug-drug interactions can be demonstrated in PK studies, only a few of these interactions (i.e., cyclosporine, disulfiram, and benzodiazepine may interact with OME) are of **clinical relevance**. It is also theoretically possible that, due to their profound and long-lasting inhibition of gastric acid secretion, PPIs may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g. ketoconazole, ampicillin esters and iron salts). These concerns need to be included in the labeling.

IV. DRUG EXPOSURE

Overall, this SU report provides data on the groups of patients listed in Table 1. The exposure data in this Table considers only those trials contributing complete safety data [A001-309, E044-310, A001-118, A001-501, and E033-311]. The sponsor notes that a total of 6,000,000 patient

days of Aciphex™ exposure have been reported in post-marketing surveillance in Japan. Although not included in the numbers in Table 1, SAEs and premature discontinuations due to AEs have been compiled from an additional 88 patients treated with Aciphex™ in the European Study #033-116.

TABLE 1
NDA 20-973

RABEPRAZOLE SAFETY DATABASE
(SU)

Treatment	Total No. of Patients	Dosage & Duration and Study Population	No. of Pts.
ACIPHEX™	546	a) 10 mg/day for at least 2 years in GERD Maintenance Extension trials[a]	135
		b) 20 mg/day for at least 2 years in GERD Maintenance Extension trials[b]	157
		c) 10 mg BID (counted as 20 mg/day) for up to 8 weeks in an acute GERD trial[c]	103
		d) 20 mg BID for up to 8 weeks in an acute GERD trial[d]	104
		e) 60 to 120 mg/day over an average duration of 1.25y in pts. with idiopathic GAHS or ZES[e]	11
		f) Normal, healthy volunteers treated with 10 mg (one dose per week) in a four period crossover bioequivalence trial	36
			546
PL	27		
OME	167		
GRAND Total in SU	740		

a,b) Studies E3810-A001-309 and E3810-E044-310
c,d) Study E3810-E033-311
e) Study –501

In the studies included in Table 1, total exposure to RABE sodium exceeded 702 patient years; out of these, 238 patients received 10 mg RABE OD (for 316 patient years) and 103 patients were on a 10 mg BID dose-regimen. RABE 20 mg OD was received by 261 patients for >386 patient years. Study 501 is a dose-titration study in 11 patients with idiopathic GAHS or ZES; these patients received total doses of RABE sodium ranging from 60 to 120 mg. Additionally, in the bioequivalence study in 36 healthy young volunteers, 10 mg doses of RABE sodium were administered in a crossover design.

V. DISPOSITION OF PATIENTS (TABLE 2)

This Table presents a summary of patient disposition data for studies E3810-A001-309 and E3810-E044-310 Extension trials. All in all, the proportion of patients discontinuing prematurely was similar between RABE sodium and PL in one trial and between RABE sodium and OME in the other. In one trial for the second year extension, the proportion of patients discontinued due to AEs was numerically higher in the RABE sodium groups when compared to the PL group; however, these differences do not appear to be clinically meaningful. On the other hand, the other trial showed comparability between the RABE groups and OME for both the first and the second year extension in the proportion of patients that withdrew because of AEs.

In addition, the sponsor noted that 12 patients in the 10 mg Aciphex™ group, and 6 in the 20 mg Aciphen™ group continued into the third year of the extension study –309. There were no patients continued into the PL group. Two patients in the 10 mg group, and 1 in the 20 mg group completed the study. No patients in either group withdrew due to AEs. Ten patients in the 10 mg group, and 4 in the 20 mg group withdrew for 'Other' reasons. Additionally, 1 patient in the 20 mg group withdrew for lack of efficacy (Sponsor's Appendix 1, Table 8).

TABLE 2
NDA 20-973 SU

Patient Disposition Summary
Study E3810-A001-309 and E3810-E044-310 Extension Trials

Extension Study # / Disposition	Aciphex™ Sodium (mg)		OME (mg)	PL
	10	20	20	
E3810-A001-309 (1 Year Extension)				
Number of Subjects	69	93	NA	27
Completed The Study	66 (95.7%)	79 (84.9%)		23 (85.2%)
Discontinued Prematurely	3 (4.3%)	14 (15.1%)		4 (14.8%)
Adverse Events	0	6.5%		0
Lack of Efficacy	0	1.1%		0
Lost to Follow-Up	1.4%	2.2%		0
Other	2.9%	5.4%		14.8%
E3810-A001-309-2 (2 Year Extension)				
Number of Subjects	62	75	NA	23
Completed The Study	47 (75.8%)	64 (85.3%)		17 (73.9%)
Discontinued Prematurely	15 (24.2%)	11 (14.7%)		6 (26.1%)
Adverse Events	4.8%	4.0%		0
Lack of Efficacy	1.6%	1.3%		0
Lost to Follow-Up	1.6%	1.3%		0
Other	16.1%	8.0%		26.1%
E3810-E044-310 (1 Year Extension)				
Number of Subjects	66	64	64	NA
Completed The Study	63 (95.5%)	59 (92.2%)	56 (87.5%)	
Discontinued Prematurely	3 (4.5%)	5 (7.8%)	8 (12.5%)	
Adverse Events	0	1.6%	6.3%	
Lack of Efficacy	0	0	0	
Lost to Follow-Up	1.5%	1.6%	1.6%	
Other	3.0%	4.7%	4.7%	
E3810-E044-310-2 (2 Year Extension)				
Number of Subjects	63	59	55	NA
Completed The Study	62 (98.4%)	58 (98.3%)	54 (98.2%)	
Discontinued Prematurely	1 (1.6%)	1 (1.7%)	1 (1.8%)	
Adverse Events	1.6%	0	1.8%	
Lack of Efficacy	0	0	0	
Lost to Follow-Up	0	0	0	
Other	0	1.7%	0	

Data Source: Sponsor's Tables 8 (Volume 2, Appendix 1, p. 11); 9 (Volume 2, Appendix 1, p. 12)

VI. DEATHS

- There were no deaths reported in clinical trials from February 4, 1998 (cut-off for NDA for deaths) through August 31, 1998.

- Post-marketing safety surveillance in Japan from October 14, 1997 (the International Birth Date of PARIET™) through August 31, 1998 revealed 2 deaths (Table 3). The first

(rhabdomyolysis) was unrelated to Aciphex™. In this reviewer's opinion, the second (sudden death in a relatively young person with no reported Hx of cardiovascular disorder and no apparent confounding medications) was possibly related to the drug. Temporal relationship to the drug appeared to exist. This event of sudden death should be included in the labeling.

TABLE 3
NDA 20-973 SU

Japanese Post-Marketing Reports of Death from
October 14, 1997 through August 31, 1998

ARIS No. Pt. Ident.	Total Daily Dose of Aciphex™ (mg)	Duration of Exposure[a] (Days)	Cause and Date of Death	Relationship to Tx With Aciphex™ R/S	Reviewer
J-IRS-000043[b] I-Y, 85M	20	9	Rhabdomyolysis (March 25, 1998)	R: Unrelated S: Unrelated	**NOT**
J-IRS-000049[c] S-H, 45M	20	27	**Sudden death (April 7, 1998)**	R: Unlikely S: Possibly	**POSS**

R = Reporter S = Sponsor

a) At the time of the event.
b) Location of complete narrative: Sponsor's Vol. 4; Appendix 2; Pg. 1
c) Location of complete narrative: Sponsor's Vol. 4; Appendix 2; Pg. 3

Narrative on Aris No. J-IRS-000049

On April 7, 1998, this 45-y old Japanese M with no reported Hx of CV disorder died while sleeping.

Approximately one month earlier, on March 8, 1998, he developed an acute abdomen, was admitted to the hospital, and was found to have a DU. Tx was started with fasting and FAM 2amps/day I.V. for 3 days. On March 11, 1998, Aciphex™ 20 mg daily PO was prescribed, and 7 days later ecabet sodium 3 gm daily was added to the Tx regimen. The patient was discharged from the hospital 5 days later, on March 23, 1998. Four days post-discharge, on March 27, 1998, the patient underwent endoscopy which revealed healing of the DU and the presence of *H. pylori*. The patient then began a 7-day course of amoxicillin and clarithromycin to clear the infection; these medications were stopped on April 2, 1998, 5 days prior to the patient's death. Aciphex™ and ecabet sodium were D/C the day prior to death.

An autopsy revealed no organic disorder in the patient's cardiorespiratory system and no abnormal findings in any of his abdominal organs. Additionally, no abnormalities were detected in a CT scan of the head performed shortly after death. The reporting physician concluded that the cause of death was most likely **cardiac arrhythmia**.

VII. SERIOUS ADVERSE EVENTS (SAEs)

The information reviewed here is on new and cumulative events reported from February 3, 1998 through August 31, 1998.

- No SAEs were reported in healthy volunteers or patients in the short-term trials E3810-A001-118, E3810-A001-501, E3810-E033-116 or E3810-E033-311.

- The sponsor presented a Table (6.3) listing all 15 Aciphex™-treated patients, mostly 20 mg/day [GERD=14; these were participating in the long-term extension trials E3810-A001 -309, -309-1 or –309-2 (North American studies), or E3810-E044-310 or –310-1 (European studies), ZES=1] who reported 16 SAEs. An additional Table (6.4) listed 2 OME-treated patients who reported SAEs.

  - Included among Aciphex™-treated patients were: adenocarcinoma, chest pain (see below), appendicitis, bile leak, pancreatitis, prostate resection and urogenital disorder. The two OME cases consisted of biliary pain and acute appendicitis.

  - Each was considered to be unrelated to Tx by both the PI and the sponsor. This reviewer agrees with this assessment.

  - There were 3 cases of chest pain [1 F (severe), 2 M] and 1 case of moderate angina pectoris. All occurred at least 921 days after the start of Aciphex™ 20 mg/day. One occurrence of chest pain which led to the D/C of Aciphex™ was considered to be gastrointestinal in origin (Pt. 006/19708 in study E3810-A001-309-1).

NOTE: A cumulative total of **147** unique Aciphex™-treated patients **(134+13)**[3] experienced one or more SAEs in clinical trials through August 31, 1998. This incidence is similar to that reported for the prior cut-off date of February 3, 1998 (134 patients, 3.8%, n=3556; ISS Section 6.3, NDA Volume 249, page 294).

There were no further SAEs in patients receiving PL (cumulative total = 10), and only two more in OME-treated patients (cumulative total 25+2 = 27) (ISS Section 6.3, NDA Volume 249, page 294). No patient received RAN or FAM during the update reporting.

- The sponsor also presented (in Table 6.5) additional information that was received for a number of SAEs after the NDA in March 1998. Of greatest importance was the **rechallenge study** in patient A001-108 with hepatic dysfunction who developed hepatic **encephalopathy** during a Phase I study of Aciphex™. This rechallenge is discussed in detail in sponsor's Section 6.7.3.1. For the remainder of these events, the interpretation of causality was not altered by the updated data. None was considered to be related to Tx

[3] 2 of the 15 Aciphex™-treated patients who experienced SAEs since the prior cut-off date of February 3, 1998 also experienced an SAE which was reported in the original ISS dated March 15, 1998. Therefore, the total number of new Aciphex™-treated patients with SAEs is 13.

with Aciphex™. In most cases, the additions and/or corrections were trivial or reported a final resolution for the event (sponsor's Appendix 2).

A. Post-Marketing Safety Surveillance SAEs

The sponsor's Table 6F listed the SAEs reported in Japan since the International Birth Date of Pariet™ (October 14, 1997), sorted by COSTART body system and preferred term.[4] In addition to the sudden death previously mentioned, the following SAEs were considered to be at **least possibly related** to Tx with Aciphex™ by either the reporter, the sponsor, or both:

- blood dyscrasias (thrombocytopenia, n=9 of 10 reported; leukopenia, n=3[a]; pancytopenia, n=1)
- hepatic dysfunction (jaundice, n=1; abnormal liver function tests, n=4)
- coma and hyperammonemia (n=1)
- overdose associated with disorientation and delirium (n=1)[b]
- cardiovascular events (complete heart block, n=1; bradycardia, n=1)
- possible hypersensitivity reactions (interstitial pneumonia and elevated liver enzymes, n=1; erythroderma and swelling of acro-extremities, n=1; dermatitis, n=1; eczema, generalized edema, and blisters, n=1)

a) Temporal relationship and (+) dechallenge.
b) (+) rechallenge in the MTL's opinion.

From the evaluation of the narrative of each of the events listed above and summarized in sponsor's Tables 16.6, 6.7 and 6.8, this reviewer concludes that the following events were probably or unlikely NOT related to Aciphex™: 5 of the 9 cases of thrombocytopenia, 1 of the 4 cases of LFTs abnormal, and the one case of complete heart block; bradycardia [a temporal relationship did not exist because the event was diagnosed nearly 6 weks after the D/C of the drug]. In all remaining cases, there was at least a possible (in some cases probable) relationship to the drug. These terms (minus the complete heart block and bradycardia) should be incorporated in the labeling, in a Section dealing with post-marketing safety surveillance information.

VIII. CUMULATIVE INCIDENCE OF DISCONTINUATIONS DUE TO AES THROUGH AUGUST 31, 1998

A cumulative total of **114** unique Aciphex™-treated patients **108+6** discontinued clinical trials because of AEs. This incidence is slightly higher than that reported for the prior cut-off date of February 3, 1998 (108/3556, 3.0%). The most frequent treatment-emergent AEs leading to discontinuation[5] of Aciphex™ remained

vomiting (n=5)
abdominal pain (n=4)
rash (n=4)

[4] Those submitted as expedited reports to FDA were identified by their serial submission number(s).
[5] Sponsor's NDA Table 6I, ISS, vol. 249, p. 355