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Clinical Trial Synopsis LAN-0003-0041, NCT# 00175032

Name of Company: TAP Pharmaceutical Products Inc.

Name of Finished Product: Lansoprazole

Name of Active Ingredient: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole

Title of Study: A Randomized, Double-Blind, Phase 3 Study to Compare the Efficacy and Safety of Lansoprazole 30 mg QD and Naproxen 500 mg BID versus Celecoxib 200 mg QD in Risk Reduction of Non-Steroidal Anti Inflammatory Associated Ulcers in Osteoarthritis Subjects Taking Low Dose Aspirin

Investigators Who Enrolled Subjects: 81 in the United States (US)

Study Centers That Enrolled Subjects: 81 sites in the US

Publication (Reference): Goldstein JL, Cryer B, Amer F, Hunt B. Celecoxib plus aspirin versus naproxen and lansoprazole plus aspirin: a randomized, double-blind, endoscopic trial. Clin Gastroenterol Hepatol. 2007;5(10):1167-1174. TAP-07-012892

Study Period:

Date of First Dose: 22 July 2003

Date of Last Procedure: 28 July 2004

Phase of Development: 3

Objective: The objective of this 12-week study was to compare the gastroduodenal ulceration rate, gastrointestinal (GI) complication rate, and the incidence of nonsteroidal anti-inflammatory drug (NSAID)-associated dyspepsia at the end of 12 weeks of treatment with celecoxib 200 mg once daily (QD) versus concomitant administration of lansoprazole 30 mg QD and naproxen 500 mg twice daily (BID) in osteoarthritis (OA) subjects taking low-dose aspirin.

Methodology: This was a Phase 3, multicenter, double-blind, parallel, active drug-controlled, randomized study. One thousand forty-five subjects who had OA and were taking low-dose aspirin were randomized in a 1:1 ratio to receive 1 of the following 2 treatment regimens:

- 1) Lansoprazole 30 mg QD, naproxen 500 mg BID, and aspirin 81 mg or 325 mg QD; or
- 2) Celecoxib 200 mg QD and aspirin 81 mg or 325 mg QD

The duration of the study was a maximum of 14 weeks, which included a Screening Period of up to 2 weeks and a Treatment Period of 12 weeks. Subjects began taking study drugs within 24-72 hours following the Screening endoscopy and continued to self-administer the study drugs for 12 weeks. Lansoprazole, naproxen, and celecoxib were provided as double-blind study medications; aspirin was provided as an open-label study drug, and the dose was determined by the investigator. Open-label Gelusil was provided for dyspepsia symptom rescue. Subjects returned for study visits after 4, 8, and 12 weeks of treatment. Endoscopy was repeated at Week 12.

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Number of Subjects (Planned and Analyzed): 960 subjects were planned, 1045 were analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects were ≥ 18 years of age, required the chronic use of NSAIDs for treatment of OA, and required low-dose aspirin for cardiovascular prophylaxis. Subjects were also free from gastroduodenal ulcers and did not have ≥ 10 gastroduodenal erosions or a GI bleed within the past year.

Duration of Treatment: 12 weeks

Test Product, Dose and Mode of Administration, Batch Number:

Test Product	Dose/Frequency	Formulation	Mode of Administration	Commercial Lot Number	Finishing Lot Number
Lansoprazole	30 mg QD	30-mg capsule	Oral	OMYK979	030013
Naproxen	500 mg BID	500-mg tablet ^a	Oral	E1702	020093

Reference Therapy, Dose and Mode of Administration, Batch Number:

Celecoxib	200 mg QD	100-mg capsule	Oral	C200080	020098
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Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the proportion of subjects in each treatment group with gastroduodenal ulcers at the Final Visit.

Secondary efficacy variables included the following:

- Proportion of subjects in each treatment group with GI complications and with each type of GI complication;
- The severity of each dyspepsia symptom and combined dyspepsia score at Week 4, 8, and 12 as collected on the Dyspepsia Questionnaire;
- The proportion of subjects in each treatment group with dyspepsia at Weeks 4, 8, and 12 who did not have dyspepsia at Baseline;
- The proportion of subjects in each treatment group without dyspepsia at Weeks 4, 8, and 12 who had dyspepsia at Baseline;
- The scores of each Severity of Dyspepsia Assessment (SODA) Questionnaire scale for subjects with dyspepsia at each respective visit;
- The change from Baseline of each SODA Questionnaire scale at each visit for subjects with dyspepsia at Baseline.

Two additional secondary efficacy endpoints were added to the statistical analysis plan later in the clinical trial lifecycle: severity of joint pain at Weeks 4, 8, and 12 and ulcer size for those who had an endoscopy-proven ulcer.

All primary and secondary efficacy analyses were performed on the modified intent-to-treat (MITT) population. The MITT subjects were defined as all subjects who were enrolled in the study, who took at least 1 dose of study drug, and who had neither a gastroduodenal ulcer nor at least 10 erosions at Baseline. In addition, only those subjects who had at least 1 postbaseline measurement were included in the analysis of the respective efficacy variable. Unless otherwise specified, p-values ≤ 0.050 were considered statistically significant.

Criteria for Evaluation:

Safety:

The safety of study drug was assessed throughout the study by laboratory tests, physical examinations, concomitant medication use, vital signs results, and monitoring of adverse events. All randomized subjects who received at least 1 dose of study drug were included in the safety analyses.

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Statistical Methods:

Efficacy:

Comparison of the primary efficacy variable, the proportion of MITT subjects with gastroduodenal ulcers at the Final Visit, was made between the treatment groups using Fisher's exact test. Comparisons of the proportion of subjects with GI complications and with each type of GI complication (GI bleeding, perforations, and gastric outlet obstructions) between treatment groups were made using Fisher's exact test.

The severities of each dyspepsia symptom collected using the Dyspepsia Questionnaire (abdominal pain, nausea, vomiting, heartburn, fullness, and belching) were summarized by tabulation of the severities of each symptom at each postbaseline visit by Baseline severity for each treatment group. The severities of each symptom at each visit were compared between treatment groups using CMH methodology with Baseline symptom severity as the stratification factor.

The combined dyspepsia score was defined as the sum of the severities of each of the individual dyspepsia symptoms. The mean change from Baseline to each visit was computed for the combined dyspepsia score. A comparison of the mean change was made between treatment groups at each visit using a one-way analysis of variance (ANOVA) with treatment group as the factor.

Subjects were classified at Baseline and at each visit as having dyspepsia based on the Dyspepsia Questionnaire. For subjects with no Baseline dyspepsia, comparisons were made between the treatment groups of the proportion of subjects with dyspepsia at each postbaseline visit using Fisher's exact test. For subjects that did have dyspepsia at Baseline, treatment comparisons were made of the proportion of subjects with no dyspepsia at the postbaseline visits.

The SODA Questionnaire was evaluated for subjects with dyspepsia at Baseline by comparing the scores at each visit and the mean change from Baseline to each visit between the treatment groups for each of the SODA scales (pain and nonpain symptoms, and satisfaction) using one-way ANOVA.

This study included a single interim analysis (on the primary endpoint only) carried out using the available endoscopic data on the first 480 subjects who completed the double-blind treatment portion of this study. Based on the results of this interim analysis, the study was continued and no adjustment of sample size was necessary.

Safety:

The number and percentage of subjects with treatment-emergent adverse events were summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and high level term for each treatment group. Separate summaries were also generated for treatment-related (possibly, probably, or definitely related) adverse events. Comparisons between the treatment groups were made with Fisher's exact test.

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Summary and Conclusions:

Baseline Demographics and Characteristics:

There were no statistically significant differences in the Baseline demographics between the 2 treatment groups for either the All Subjects or MITT populations. Demographic variables for the 1045 subjects (All Subjects) and for the 1014 MITT subjects, are summarized in the following table.

Baseline Demographics Variable	All Subjects		MITT Subjects	
	Celecoxib 200 mg QD N=516	Lansoprazole 30 mg QD and Naproxen 500 mg BID N=529	Celecoxib 200 mg QD N=502	Lansoprazole 30 mg QD and Naproxen 500 mg BID N=512
Race [n (%)]				
Asian	13 (2.5)	10 (1.9)	13 (2.6)	10 (2.0)
Black	76 (14.7)	65 (12.3)	74 (14.7)	62 (12.1)
Caucasian	363 (70.3)	392 (74.1)	352 (70.1)	379 (74.0)
Hispanic	56 (10.9)	54 (10.2)	55 (11.0)	54 (10.5)
Other	8 (1.6)	8 (1.5)	8 (1.6)	7 (1.4)
Age (years)				
N	516	529	502	512
Mean (SD)	56.7 (10.84)	56.7 (11.49)	56.8 (10.81)	56.8 (11.55)
Minimum-Maximum	22-83	18-87	22-83	18-87
Gender [n (%)]				
Male	169 (32.8)	192 (36.3)	165 (32.9)	190 (37.1)
Female	347 (67.2)	337 (63.7)	337 (67.1)	322 (62.9)
Weight (pounds)				
N	516	529	502	512
Mean (SD)	190.6 (51.43)	191.9 (46.79)	191.0 (51.75)	191.8 (46.44)
Minimum-Maximum	90-464	100-350	90-464	100-350
Height (inches)				
N	515	528	501	511
Mean (SD)	65.9 (4.21)	65.9 (3.84)	65.9 (4.23)	65.9 (3.84)
Minimum-Maximum	49-78	52-77	49-78	52-77
BMI (kg/m²)				
N	515	528	501	511
Mean (SD)	30.9 (8.07)	31.1 (7.14)	31.0 (8.13)	31.1 (7.16)
Minimum-Maximum	17-84	17-59	17-84	17-59

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Summary and Conclusions (Cont):

Baseline Demographics and Characteristics (Cont):

Relevant upper GI ulcer and endoscopy-proven erosion baseline characteristics for All Subjects and MITT Subjects are summarized in the following table.

Baseline Characteristics Variables	All Subjects		MITT Subjects	
	Celecoxib 200 mg QD N=516	Lansoprazole 30 mg QD and Naproxen 500 mg BID N=529	Celecoxib 200 mg QD N=502	Lansoprazole 30 mg QD and Naproxen 500 mg BID N=512
History of Upper GI Ulcer n (%)				
Yes	47 (9.1)	58 (11.0)	47 (9.4)	58 (11.3)
No	469 (90.9)	471 (89.0)	455 (90.6)	454 (88.7)
History of Gastric Ulcer n (%)				
Yes	39 (7.6)	44 (8.3)	39 (7.8)	44 (8.6)
No	477 (92.4)	485 (91.7)	463 (92.2)	468 (91.4)
History of Duodenal Ulcer n (%)				
Yes	16 (3.1)	23 (4.3)	16 (3.2)	23 (4.5)
No	500 (96.9)	506 (95.7)	486 (96.8)	489 (95.5)
History of Esophageal Ulcer n (%)				
Yes	4 (0.8)	8 (1.5)	4 (0.8)	8 (1.6)
No	512 (99.2)	521 (98.5)	498 (99.2)	504 (98.4)
History of Upper GI Ulcer with Bleeding n (%)				
Yes	4 (0.8)	10 (1.9)	4 (0.8)	10 (2.0)
No	512 (99.2)	519 (98.1)	498 (99.2)	502 (98.0)
History of Upper GI Ulcer Associated with NSAID Use n (%)				
Yes	18 (3.5)	21 (4.0)	18 (3.6)	21 (4.1)
No	498 (96.5)	508 (96.0)	484 (96.4)	491 (95.9)
Number of Erosions at Baseline Endoscopy n (%)				
0	401 (77.7)	414 (78.3)	401 (79.9)	414 (80.9)
>0-5	80 (15.5)	75 (14.2)	80 (15.9)	75 (14.6)
>5-10	21 (4.1)	23 (4.3)	21 (4.2)	23 (4.5)
>10	0	0	0	0

Note: Upper GI ulcer includes gastric ulcer, duodenal ulcer, and esophageal ulcer.

Note: No statistically significant differences between treatment groups were observed.

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Summary and Conclusions (Cont):

Subject Disposition:

The disposition of subjects who participated in this study are summarized in the following table.

	Celecoxib 200 mg QD	Lansoprazole 30 mg QD and Naproxen 500 mg BID	All Subjects
All Subjects	516	529	1045
MITT Subjects^a	502 (97.3%)	512 (96.8%)	1014 (97.0%)
Subjects Excluded from MITT^b	14 (2.7%)	17 (3.2%)	31 (3.0%)
Completed Study	437 (84.7%)	445 (84.1%)	882 (84.4%)
Prematurely Discontinued From the Study	79 (15.3%)	84 (15.9%)	163 (15.6%)
Timing of Premature Discontinuations (weeks)			
<4	43 (8.3%)	36 (6.8%)	79 (7.6%)
4 to <8	23 (4.5%)	28 (5.3%)	51 (4.9%)
8 to <12	11 (2.1%)	18 (3.4%)	29 (2.8%)
≥12	2 (0.4%)	2 (0.4%)	4 (0.5%)
Primary Reason for Premature Discontinuation:			
Adverse event	33 (6.4%)	35 (6.6%)	68 (6.5%)
Protocol violation	11 (2.1%)	6 (1.1%)	17 (1.6%)
Personal reason(s)	5 (1.0%)	8 (1.5%)	13 (1.2%)
Lost to follow-up	7 (1.4%)	5 (0.9%)	12 (1.1%)
Developed gastrointestinal or duodenal ulcer, or GI Complication	1 (0.2%)	0	1 (0.1%)
Inadequate joint pain control	5 (1.0%)	6 (1.1%)	11 (1.1%)
Too many GI symptoms	6 (1.2%)	7 (1.3%)	13 (1.2%)
Other	11 (2.1%)	17 (3.2%)	28 (2.7%)

a Subjects randomized who received at least one dose of study drug, and had neither a gastroduodenal ulcer nor ≥10 erosions at Baseline.

b Subjects with no endoscopy results within Days -3 to 1.

Efficacy Results:

The incidence of endoscopy-proven gastroduodenal ulcers after 12 weeks of treatment (at Final Visit) in OA subjects requiring low-dose aspirin for cardiovascular prophylaxis is presented in the following table.

Analysis	Lansoprazole 30 mg QD		Statistically Significant (p-Value)
	Celecoxib 200 mg QD n/N (%)	and Naproxen 500 mg BID n/N (%)	
Primary Analysis	42/426 (9.9)	38/428 (8.9)	No (p=0.640)

Note: Subjects must have had at least one postbaseline endoscopy to be included in these analyses.

Note: p-values were from Fisher's exact test.

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Summary and Conclusions (Cont):

Efficacy Results (Cont):

There were no statistically significant differences between the treatment groups in either the incidence of GI complications or the incidence of any particular category of GI complication as shown in the following table.

GI Complication Type	Celecoxib 200 mg QD n/N (%)	Lansoprazole 30 mg QD and Naproxen 500 mg BID n/N (%)
GI Complication	0/473 (0)	1/494 (0.2)
GI Bleeding	0/473 (0)	1/494 (0.2)
Perforation	0/423 (0)	0/494 (0)
Gastric Outlet Obstruction	0/473 (0)	0/494 (0)

There was a statistically significant difference between the treatment groups in the distribution of severity scores (none, mild, moderate, or severe) for heartburn at Weeks 4, 8, and 12, adjusting for the Baseline severity score ($p < 0.001$ at all visits). At these visits, lower proportions of subjects in the lansoprazole/naproxen treatment group reported heartburn symptoms as present, and as moderate to severe rather than mild, than did subjects in the celecoxib group. In addition, there was a statistically significant difference between the treatment groups in the distribution of severity scores for vomiting at Week 4 only ($p = 0.044$), with a lower proportion of subjects in the lansoprazole/naproxen treatment group reporting vomiting symptoms as present (mild to moderate). There were no statistically significant differences between the treatment groups in the distribution of severity scores for the other individual dyspepsia symptoms (abdominal pain, fullness, nausea).

There was a statistically significantly higher mean change from Baseline in combined severity of dyspepsia scores for the Dyspepsia Questionnaire at Weeks 4 and 12 in the celecoxib group compared to the lansoprazole/naproxen group as shown in the following table:

Study Week	Celecoxib 200 mg QD		Lansoprazole 30 mg QD and Naproxen 500 mg BID		Statistically Significant Change from Baseline (p-Value)
	Actual Dyspepsia Severity Score Mean (SD)	Change of Dyspepsia Severity Score from Baseline Mean (SD)	Actual Dyspepsia Severity Score Mean (SD)	Change of Dyspepsia Severity Score from Baseline Mean (SD)	
Baseline	1.8 (2.38)	-	1.7 (2.09)	-	-
Week 4	2.5 (2.71)	0.7 (2.35)	1.9 (2.30)	0.3 (2.35)	Yes ($p = 0.012$)*
Week 8	2.5 (2.85)	0.7 (2.36)	2.2 (2.56)	0.5 (2.62)	No ($p = 0.321$)
Week 12	2.6 (2.81)	0.8 (2.46)	2.1 (2.48)	0.5 (2.57)	Yes ($p = 0.043$)*

Note: Combined dyspepsia score is the sum of the severities (0=None; 1=Mild; 2=Moderate; 3=Severe) of each individual dyspepsia symptom (abdominal pain, nausea, vomiting, heartburn, fullness, and belching).

Note: * indicates statistical significance at the 0.05 level: p-values were from an ANOVA model with treatment as the factor.

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Summary and Conclusions (Cont):

Efficacy Results (Cont):

Among subjects without dyspepsia at Baseline, the proportion of subjects with dyspepsia at the Weeks 4, 8 and 12 visits was not statistically significantly different between the treatment groups based on results from the Dyspepsia Questionnaire as shown in the following table.

Subjects Shifting to Having Dyspepsia at^a	Celecoxib 200 mg QD n/N (%)	Lansoprazole 30 mg QD and Naproxen 500 mg BID n/N (%)	Statistically Significant (p-Value)
Week 4	99/238 (41.6)	98/269 (36.4)	No (p=0.237)
Week 8	86/238 (36.1)	102/269 (37.9)	No (p=0.713)
Week 12	95/238 (39.9)	101/269 (37.5)	No (p=0.648)

Note: p-values were from Fisher's exact test.

a Subjects did not have dyspepsia at Baseline (based on definition).

Results from the Dyspepsia Questionnaire indicated a statistically significantly higher proportion of subjects who shifted dyspepsia status from having dyspepsia at Baseline to not having dyspepsia at Weeks 4, 8, and 12 in the lansoprazole/naproxen group compared to the celecoxib group, as shown in the following table.

Subjects Shifting to No Dyspepsia at^a	Celecoxib 200 mg QD n/N (%)	Lansoprazole 30 mg QD and Naproxen 500 mg BID n/N (%)	Statistically Significant (p-Value)
Week 4	40/220 (18.2)	66/212 (31.1)	Yes (p=0.002)**
Week 8	32/220 (14.5)	69/212 (32.5)	Yes (p<0.001)***
Week 12	42/220 (19.1)	67/212 (31.6)	Yes (p=0.003)**

Note: **, *** indicates statistical significance at the 0.01 and 0.001 level, respectively. p-values were from Fisher's exact test.

a Subjects had dyspepsia at Baseline (based on definition).

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Summary and Conclusions (Cont):

Efficacy Results (Cont):

The mean scores for the scales of the SODA Questionnaire at each visit are shown in the following table.

Mean Severity of Dyspepsia Assessment Scale	Celecoxib 200 mg QD			Lansoprazole 30 mg QD and Naproxen 500 mg BID			Statistically Significant (p-Value)
	N	Mean	SD	N	Mean	SD	
Pain Symptoms							
Baseline	157	16.3	9.24	142	15.8	8.66	No (p=0.608)
Week 4	194	16.7	9.46	158	18.0	8.26	No (p=0.163)
Week 8	194	16.6	8.87	165	18.5	8.73	Yes (p=0.046)*
Week 12	187	17.4	9.5	160	18.6	7.66	No (p=0.199)
Nonpain Symptoms							
Baseline	157	13.9	3.56	142	14.0	3.20	No (p=0.955)
Week 4	194	14.4	3.35	159	14.2	3.24	No (p=0.482)
Week 8	193	14.5	3.17	165	14.4	3.38	No (p=0.781)
Week 12	185	14.6	3.26	161	14.4	2.84	No (p=0.584)
Satisfaction							
Baseline	157	14.1	5.10	143	13.6	4.61	No (p=0.470)
Week 4	195	14.7	4.89	159	14.5	4.59	No (p=0.616)
Week 8	194	14.8	4.89	166	13.61	4.53	Yes (p=0.017)*
Week 12	187	15.0	4.90	161	3.5	4.21	Yes (p=0.002)**

Note: A subject was classified as having dyspepsia at a visit if either abdominal pain, nausea, vomiting, or heartburn were reported with at least a mild severity on the Dyspepsia Questionnaire.

Note: Severity of Dyspepsia Assessment completed more than 3 days after the final dose of study drug were excluded from the analysis.

Note: Subjects must have a baseline value and at least one post baseline value to be included in the analysis of the respective variable.

Note: * and ** indicates statistical significance at the 0.05 and 0.01 level, respectively: p-values were from an ANOVA model with treatment as the factor.

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Summary and Conclusions (Cont):

Efficacy Results (Cont):

The mean changes from Baseline in the scales of the SODA Questionnaire are shown in the following table.

Mean Change From Baseline in Severity of Dyspepsia Assessment Scale	Celecoxib 200 mg QD (n=157)		Lansoprazole 30 mg QD and Naproxen 500 mg BID (n=142)		Statistically Significant (p-Value)
	Mean	SD	Mean	SD	
Pain Symptoms					
Week 4	-0.2	11.28	-0.3	10.87	0.953
Week 8	0.2	9.73	-1.0	11.45	0.346
Week 12	-0.3	11.04	-1.0	11.17	0.563
Nonpain Symptoms					
Week 4	0.4	3.60	-0.5	3.80	0.025*
Week 8	0.4	3.29	-0.7	3.82	0.007**
Week 12	0.1	3.86	-0.7	3.75	0.069
Satisfaction					
Week 4	1.2	5.89	1.9	5.28	0.281
Week 8	0.7	6.00	1.9	5.95	0.078
Week 12	1.2	5.45	2.0	5.98	0.196

Note: A subject was classified as having dyspepsia at a visit if either abdominal pain, nausea, vomiting, or heartburn were reported with at least a mild severity on the Dyspepsia Questionnaire.

Note: Severity of Dyspepsia Assessment completed more than 3 days after the final dose of study drug were excluded from the analysis.

Note: Subjects must have a baseline value and at least one post baseline value to be included in the analysis of the respective variable.

Note: * and ** indicates statistical significance at the 0.05 and 0.01 level, respectively: p-values were from an ANOVA model with treatment as the factor.

There was no statistically significant difference between the 2 treatment groups in the severity of joint pain experienced for Weeks 4, 8, and 12. Similarly, there was no statistically significant difference in the size of endoscopy-proven gastroduodenal ulcers between the 2 treatment groups.

Safety Results:

The incidence of treatment-emergent adverse events was 53% in the celecoxib group versus 57% in the lansoprazole/naproxen group and of treatment-related adverse events was 23% in the celecoxib group versus 25% in the lansoprazole/naproxen group. The most frequently reported treatment-emergent adverse events ($\geq 5\%$ of subjects by MedDRA Higher Level Term) in both the celecoxib and lansoprazole/naproxen groups were upper respiratory tract infections; dyspeptic signs and symptoms; flatulence, bloating, and distension; gastrointestinal and abdominal pains (excluding oral and throat); and nausea and vomiting symptoms. In addition, $\geq 5\%$ of subjects in the lansoprazole/naproxen group reported diarrhoea (excluding infective) and gastrointestinal atonic and hypomotility disorders NEC.

The greater incidence of treatment-emergent diarrhoea (excluding infective) that was observed in the lansoprazole/naproxen group (7% in the lansoprazole/naproxen group versus 4% in the celecoxib group) was statistically significant. In addition, a statistically significantly greater incidence of the following treatment-emergent adverse events were also observed in the celecoxib group versus the lansoprazole/naproxen group; dyspeptic signs and symptoms (10% versus 7%, respectively), asthenic conditions (1% versus <1%, respectively), non-site specific injuries not elsewhere classified (NEC) (4% versus <1%,

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Summary and Conclusions (Cont):

Safety Results (Cont):

respectively), and musculoskeletal and connective tissue signs and symptoms (4% versus 1%, respectively). There was also a statistically significantly greater incidence of treatment-related rashes, eruptions, and exanthems NEC in the lansoprazole/naproxen group versus the celecoxib group (6 subjects [1%] versus 0 subjects, respectively).

Ten subjects (6 in the celecoxib group and 4 in the lansoprazole/naproxen group) reported 12 serious adverse events (SAEs). One SAE in each treatment group was considered by the investigators to be possibly or probably related to treatment; all other SAEs were deemed to be unrelated to treatment. The only SAE (MedDRA Higher Level Term) observed in more than one subject was Pain and Discomfort NEC (Preferred Term of Chest Pain), which was experienced by 2 subjects (one in each group). No subjects died during the study.

There were 80 subjects (40 in each group) who prematurely discontinued due, at least in part, to adverse events. The majority of these subjects (26 in each group) discontinued due, at least in part, to gastrointestinal disorders. The other frequently reported (≥ 3 subjects) adverse events leading to premature discontinuation were nervous system disorders, musculoskeletal and connective tissue disorders, and general disorders and administration site conditions in both treatment groups, and renal and urinary disorders in the lansoprazole/naproxen group.

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