

**Table 12: Characteristics of all Lansoprazole Cases (Postmarketing)**

		Death	Serious	Non-serious	Overall
Total number of case reports		215	1349	8212	9776
Total number of adverse event terms		471	3132	14165	17768
Age, yrs	N	215	1349	8212	9776
	Mean <sup>a</sup>	69.9	56.4	56.9	57.2
	Range	0 – 97	0 - 95	0 - 99	0 – 99
Age group, yrs n(%)	<12 years	2 (0.9)	55 (4.1)	375 (4.6)	432 (4.4)
	≥12 to 17 years	0 (0.0)	13 (1.0)	75 (0.9)	88 (0.9)
	≥18 to 65 years	64 (29.8)	647 (48.0)	3218 (39.2)	3929 (40.2)
	>66 to 74 years	43 (20.0)	228 (16.9)	1131 (13.8)	1402 (14.3)
	≥ 75 years	86 (40.0)	226 (16.8)	1422 (17.3)	1734 (17.7)
	Unknown	20 (9.3)	180 (13.3)	1991 (24.2)	2191 (22.4)
Gender n(%)	Female	100 (46.5)	705 (52.3)	5210 (63.4)	6015 (61.5)
	Male	111 (51.6)	603 (44.7)	2681 (32.6)	3395 (34.7)
	Unknown	4 (1.9)	41 (3.0)	321 (3.9)	366 (3.7)
Seriousness n(%)	Not serious	0 (0.0)	0 (0.0)	8212 (100)	8212 (84.0)
	Serious	0 (0.0)	1349 (100)	0 (0.0)	1349 (13.8)
	Death	215 (100)	0 (0.0)	0 (0.0)	215 (2.2)
Report type n(%)	Literature	8 (3.7)	36 (2.7)	0 (0.0)	44 (0.5)
	Spontaneous	189 (87.9)	1283 (95.1)	8212 (100)	9684 (99.1)
	Clinical study	18 (8.4)	30 (2.2)	0 (0.0)	48 (0.5)
Case outcome n(%)	Aggravated	0 (0.0)	1 (0.1)	4 (0.0)	5 (0.1)
	Death	215 (100)	0 (0.0)	0 (0.0)	215 (2.2)
	Fetus fatal	0 (0.0)	3 (0.2)	0 (0.0)	3 (0.0)
	Fetus influenced	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
	Not recovered / not resolved	0 (0.0)	183 (13.6)	3254 (39.6)	3437 (35.2)
	Recovered	0 (0.0)	289 (21.4)	1240 (15.1)	1529 (15.6)
	Recovered / resolved with sequelae	0 (0.0)	10 (0.7)	0 (0.0)	10 (0.1)
	Recovering / resolving	0 (0.0)	130 (9.6)	477 (5.8)	607 (6.2)
	Unknown <sup>b</sup>	0 (0.0)	733 (54.3)	3236 (39.4)	3969 (40.6)
Reporter type n(%)	Health care professional <sup>c</sup>	117 (54.4)	660 (48.9)	1559 (19.0)	2336 (23.9)
	Other	59 (27.4)	278 (20.6)	75 (0.9)	412 (4.2)
	Patient/ consumer	8 (3.7)	229 (17.0)	6150 (74.9)	6387 (65.3)
	Pharmaceutica l company	30 (14.0)	168 (12.5)	396 (4.8)	594 (6.1)
	Sponsor	0 (0.0)	2 (0.1)	9 (0.1)	11 (0.1)
	Unknown	1 (0.5)	12 (0.9)	23 (0.3)	36 (0.4)

The percent basis is the total number of cases in a seriousness category or overall.

<sup>a</sup> Mean age was based on the number of cases in which age was reported

<sup>b</sup> Unknown includes outcome not mentioned, unknown and blank.

<sup>c</sup> HCP includes dentist, nurse, other health professional, pharmacist, physician and physician (general practice).

*Sponsor's table, ISS- Module 5.3.5.3, section 10.2.4*

**Table 13: Adverse Events (Non-serious, Serious, Death and Overall)  
 for Lansoprazole by MedDRA SOC (Postmarketing)**

MedDRA SOC	Count (%) <sup>a</sup>			
	Non-Serious	Serious	Death	Overall
Gastrointestinal disorders	5355 (37.8)	455 (14.5)	44 (9.3)	5854 (33.0)
General disorders and administration site conditions	2076 (14.7)	322 (10.3)	61 (13.0)	2459 (13.8)
Nervous system disorders	1487 (10.5)	311 (9.9)	20 (4.2)	1818 (10.2)
Skin and subcutaneous tissue disorders	1251 (8.8)	289 (9.2)	31 (6.6)	1571 (8.8)
Investigations	679 (4.8)	254 (8.1)	33 (7.0)	966 (5.4)
Psychiatric disorders	601 (4.2)	136 (4.3)	10 (2.1)	747 (4.2)
Musculoskeletal and connective tissue disorders	544 (3.8)	101 (3.2)	10 (2.1)	655 (3.7)
Respiratory, thoracic and mediastinal disorders	477 (3.4)	124 (4.0)	22 (4.7)	623 (3.5)
Blood and lymphatic system disorders	107 (0.8)	185 (5.9)	70 (14.9)	362 (2.0)
Metabolism and nutrition disorders	215 (1.5)	95 (3.0)	11 (2.3)	321 (1.8)
Renal and urinary disorders	188 (1.3)	119 (3.8)	12 (2.5)	319 (1.8)
Infections and infestations	187 (1.3)	87 (2.8)	32 (6.8)	306 (1.7)
Eye disorders	231 (1.6)	74 (2.4)	0	305 (1.7)
Cardiac disorders	140 (1.0)	83 (2.7)	27 (5.7)	250 (1.4)
Hepatobiliary disorders	33 (0.2)	127 (4.1)	45 (9.6)	205 (1.1)
Reproductive system and breast disorders	179 (1.3)	18 (0.6)	0	197 (1.1)
Injury, poisoning and procedural complications	114 (0.8)	61 (2.0)	7 (1.5)	182 (1.0)
Vascular disorders	116 (0.8)	49 (1.6)	11 (2.3)	176 (1.0)
Immune system disorders	77 (0.5)	88 (2.8)	5 (1.1)	170 (1.0)
Ear and labyrinth disorders	92 (0.6)	20 (0.6)	1 (0.2)	113 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (0.1)	75 (2.4)	15 (3.2)	97 (0.6)
Pregnancy, puerperium and perinatal conditions	1 (0.0)	29 (0.9)	1 (0.2)	31 (0.2)
Congenital, familial and genetic disorders	0	19 (0.6)	1 (0.2) <sup>b</sup>	20 (0.1)
Endocrine disorders	8 (0.1)	9 (0.3)	2 (0.4)	19 (0.1)
Surgical and medical procedures	0	2 (0.1)	0	2 (0.0)
<b>Total No. of AE Terms</b>	<b>14165</b>	<b>3132</b>	<b>471</b>	<b>17768</b>
<b>Total No. of Cases</b>	<b>8212</b>	<b>1349</b>	<b>215</b>	<b>9776</b>
<b>Total No. of AE Terms / Total No. of Cases</b>	<b>1.7</b>	<b>2.3</b>	<b>2.2</b>	<b>1.8</b>

<sup>a</sup> Unless otherwise indicated, all percents are calculated based on the total number of AE terms for each column

<sup>b</sup> As classified by TAP

Adapted from Sponsor's Table Module 5.3.6 p.18

AEs Associated with Serious Cases Excluding Death (Postmarketing)

Of the 9,776 cases reported for lansoprazole, 1,349 (13.9%) were serious cases associated with 3,132 AE terms (may include both serious and nonserious AE terms). Over half (52%) of the reported events for these serious cases fell within the five SOCs: Gastrointestinal disorders (14.5%, 455/3,132), General disorders and administration site conditions (10.3%, 322/3,132), Nervous system disorders (9.9%, 311/3,132) Skin and subcutaneous tissue disorders (9.2%, 289/3,132) and Investigations (8.1%, 254/3,132). Table 14 presents the serious adverse event terms at a rate of at 0.3% or more. The most commonly reported preferred terms ( $\geq 1\%$ ) from the 3,132 AE terms associated with serious cases were:

- |                         |            |                    |            |
|-------------------------|------------|--------------------|------------|
| • diarrhea              | (2.4%, 74) | • dizziness        | (1.1%, 34) |
| • pyrexia               | (1.5%, 47) | • nausea           | (1%, 33)   |
| • drug interaction      | (1.4%, 43) | • vomiting         | (1%, 33)   |
| • condition aggravated  | (1.3%, 41) | • thrombocytopenia | (1%, 33)   |
| • abdominal pain        | (1.3%, 40) | • rash             | (1%, 32)   |
| • anaphylactic reaction | (1.2%, 38) |                    |            |

These AEs are included in the current lansoprazole prescription label with the exception of condition aggravated and certain drug interactions. These AEs are also included in the prescription label of a currently marketed OTC PPI, omeprazole 20 mg. The Gastrointestinal disorders SOC had the highest number reported of AE terms for lansoprazole both overall (5,854; 33%) and for serious cases (455; 14.5%). In this SOC, the serious AE terms with the highest reported frequency ( $\geq 1\%$ ) were diarrhea (2.4%), abdominal pain (1.3%), nausea (1%), and vomiting (1%).

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**Table 14: Adverse Events Associated with Serious Cases (rate ≥ 0.3% (Postmarketing))**

<b>MedDRA SOC / Preferred Term</b>	<b>Serious, N (%)</b>
<b>Gastrointestinal disorders</b>	<b>455 (14.5)</b>
Dianthoea	74 (2.4)
Abdominal pain	40 (1.3)
Vomiting	33 (1.0)
Nausea	33 (1.0)
Colitis	27 (0.9)
Pancreatitis	17 (0.5)
Constipation	14 (0.4)
Gastric polyps	10 (0.3)
<b>General disorders and administration site conditions</b>	<b>322 (10.3)</b>
Pyrexia	47 (1.5)
Drug interaction	43 (1.4)
Condition aggravated	41 (1.3)
Asthenia	24 (0.8)
Chest pain	21 (0.7)
Fatigue	18 (0.6)
Malaise	16 (0.5)
Drug ineffective	14 (0.4)
Pain	12 (0.4)
Oedema peripheral	10 (0.3)
<b>Nervous system disorders</b>	<b>311 (9.9)</b>
Dizziness	34 (1.1)
Convulsion	26 (0.8)
Headache	22 (0.7)
Paraesthesia	13 (0.4)
Hypoesthesia	12 (0.4)
Encephalopathy	11 (0.3)
<b>Skin and subcutaneous tissue disorders</b>	<b>289 (9.2)</b>
Rash	32 (1.0)
Urticaria	29 (0.9)
Erythema multiforme	25 (0.8)
Stevens-Johnson syndrome	17 (0.5)
Pruritus	15 (0.5)
Toxic epidermal necrolysis	14 (0.4)
Dermatitis exfoliative	11 (0.3)
<b>Investigations</b>	<b>254 (8.1)</b>
Liver function test abnormal	22 (0.7)
Weight decreased	19 (0.6)
Alanine aminotransferase increased	19 (0.6)
Aspartate aminotransferase increased	17 (0.5)
Blood alkaline phosphatase increased	14 (0.4)
Blood creatine phosphokinase increased	11 (0.3)
Gamma-glutamyltransferase increased	10 (0.3)
<b>Blood and lymphatic system disorders</b>	<b>185 (5.9)</b>
Thrombocytopenia	33 (1.0)
Leukopenia	22 (0.7)
Pancytopenia	19 (0.6)
Anaemia	18 (0.6)
Agranulocytosis	17 (0.5)
Eosinophilia	10 (0.3)

Table continued:

Psychiatric disorders	136 (4.3)
Confusional state	28 (0.9)
Depression	12 (0.4)
Anxiety	12 (0.4)
Hallucination	10 (0.3)
Hepatobiliary disorders	127 (4.1)
Jaundice	28 (0.9)
Hepatitis	28 (0.9)
Respiratory, thoracic and mediastinal disorders	124 (4.0)
Dyspnoea	29 (0.9)
Renal and urinary disorders	119 (3.8)
Renal failure acute	28 (0.9)
Nephritis interstitial	15 (0.5)
Renal impairment	10 (0.3)
Renal failure	10 (0.3)
Musculoskeletal and connective tissue disorders	101 (3.2)
Myalgia	11 (0.3)
Muscular weakness	10 (0.3)
Metabolism and nutrition disorders	95 (3.0)
Dehydration	20 (0.6)
Anorexia	14 (0.4)
Hyponatraemia	10 (0.3)
Immune system disorders	88 (2.8)
Anaphylactic reaction	38 (1.2)
Hypersensitivity	26 (0.8)
Infections and infestations	87 (2.8)
Sepsis	11 (0.3)
Cardiac disorders	83 (2.7)
Palpitations	10 (0.3)
Myocardial infarction	10 (0.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	75 (2.4)
Gastric cancer	14 (0.4)
Eye disorders	74 (2.4)
Vision blurred	15 (0.5)
Injury, poisoning and procedural complications	61 (2.0)
Injury	13 (0.4)
Fall	13 (0.4)
Vascular disorders	49 (1.6)
Hypotension	10 (0.3)
<b>Total terms (col %)</b>	<b>3132 (100)</b>

The percent basis is the total number of terms in a seriousness category.

<sup>a</sup>Total is those for the entire dataset, not just the data displayed in the table

*Sponsor's Table Module 5.3.5.3 – ISS table 10-6 p.88*

For most of the serious AEs in which causality was assessed as possible by manufacturer or reporter, there were other factors within the report that may possibly be viewed as confounders for the event such as presence of co-suspect/concomitant medications that may provide a more likely explanation for symptoms, or presence of underlying disease or possible preexisting condition(s).

In the majority of cases reported as 'condition aggravated', it appears that the condition being reported was not the underlying condition being treated with lansoprazole; the term 'condition aggravated' was often used to capture concomitant disease aggravation, rather than aggravation of underlying illness/indication for lansoprazole.

*Medical Officer Comments: Most of the serious adverse events that were presented from this database have already been previously reported either during clinical trials and/or postmarketing, and are already included in the lansoprazole prescription label. The majority of reported events were mild, self-limiting, and non-serious, and the most frequent events were related to the Gastrointestinal SOC (diarrhea, nausea and abdominal pain) or drug ineffective.*

*In cases where causality was assessed as possible by manufacturer or reporter, there were other factors within the report that may possibly be viewed as confounders for the event such as presence of co-suspect/concomitant medications that may provide a more likely explanation for symptoms, or presence of underlying disease or possible preexisting condition(s), or the information provided was too limited to allow for a meaningful interpretation. The majority of these cases either had duration of lansoprazole use of longer than 14 days (the proposed use in this application) or duration was not specified. In addition, these SAEs are similar to the SAEs identified during the Rx-to-OTC switch review of the currently marketed PPI, omeprazole.*

*The postmarketing reports did not identify any particular safety signal linked to the use of lansoprazole.*

#### Deaths from Postmarketing Data

There were 215 cases of death with associated 471 AE terms (see Table-10-10) reported for lansoprazole during postmarketing. The largest number (40%) of reports with an outcome of death was for the age group of  $\geq 75$  years (males, 51.6% and females, 46.5%). More than one-third (80, 37.2%) of all death cases were received from Japan, and 9 (4%) cases from Colombia.

In over half (53.7%) of reports of death, the reported events fell within the five SOCs: Blood and lymphatic system disorders, General disorders and administration site conditions, Hepatobiliary disorders, Gastrointestinal disorders, and Investigations. The most frequently reported event for cases with an outcome of death was condition aggravated (4.2%); it appears that this term was often used to capture concomitant disease aggravation, rather than aggravation of underlying illness/indication for lansoprazole. Table A-1 in the Appendix section contains a list of the preferred AE terms associated with fatal cases that occurred at a rate of at least 0.3%. The most commonly reported AE terms for death cases that occurred at a rate of  $\geq 1\%$  were:

• condition aggravated	(20, 4.2%)	• anemia	(7, 1.5%)
• thrombocytopenia	(11, 2.3%)	• pyrexia	(7, 1.5%)
• pneumonia	(10, 2.1%)	• hepatitis	(7, 1.5%)
• agranulocytosis	(10, 2.1%)	• jaundice	(7, 1.5%)
• pancytopenia	(10, 2.1%)	• cardiac arrest	(6, 1.3%)
• leucopenia	(10, 2.1%)	• myocardial infarction	(6, 1.3%)
• sepsis	(9, 1.9%)	• diarrhea	(6, 1.3%)
• interstitial lung disease	(9, 1.9%)	• rash	(6, 1.3%)
• Toxic Epidermal Necrolysis	(9, 1.9%)	• cardiac failure	(5, 1.1%)
• multi-organ failure	(8, 1.7%)	• renal failure	(5, 1.1%)
• death	(8, 1.7%)	• renal failure acute	(5, 1.1%)
• Steven Johnson Syndrome	(8, 1.7%)		

*Medical Officer Comments: All of the above six adverse events involving the hematologic SOC (marrow depression and hypoplastic anemias, thrombocytopenias, neutropenias, leukopenias, anemias and coagulopathies) have been reported in association with lansoprazole use. In the current lansoprazole prescription label, anemia is listed as an adverse experience occurring in less than 1% of patients or subjects who received Prevacid in domestic trials; while thrombocytopenia, leukopenia, pancytopenia, agranulocytosis and platelet count decreased are listed on the section on postmarketing adverse reactions.*

Of the 215 cases of death identified, one case involved lansoprazole injection and was inadvertently coded to the tablet NDA. Death cases were categorized as described below:

- Category 1: No documentation of confounding factors leading to death or a case in which lansoprazole could not be reasonably excluded as a factor possibly contributing to the outcome of death.
- Category 2: Confounding factors are documented that may possibly have contributed to the outcome of death (e.g., significant use of concomitant or co-suspect medications, use of nicotine or alcohol which may have contributed to the events leading up to the patient's death; underlying comorbidities or a pre-existing medical history which may have contributed to the patient's death (e.g., pre-existing malignancies); previous hospitalizations which may have predisposed the patient to the events leading up to the reported death or aggravation of pre-existing conditions which resulted in a patient's death.
- Category 3: A poorly documented case where a relationship between lansoprazole use and outcome of death could not be determined.

Of the 214 reported death cases, 71% (152/214) were categorized as Category 2, 24% (52/214) were Category 3 and 5% (10/214) were Category 1. Of the 10 cases classified as Category 1, one was a 3-month old infant on lansoprazole for GERD who died due to sudden infant death syndrome (SIDS). The other nine cases are presented below:

- A 28 y/o female (TAP1999Q01071) who took her first dose of lansoprazole in the morning (dose unknown), experienced anaphylactic shock, and died. No additional information was available.

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Prevacid® 24HR (lansoprazole 15 mg) Delayed Release Capsule

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The reporter was unable to assess causality.

- A 92 y/o female (XXX0RADR24821) with history of osteoporosis, dementia and lumbar syndrome was treated with lansoprazole for 8 days and experienced a fracture of the neck of the femur and later died of left cardiac failure. While the reporting physician did not see any causality with lansoprazole, this case was conservatively included in the category 1 cases because of the patient's lack of cardiac history and temporal relationship with lansoprazole.
- An 84 y/o male (TCI2000A02631) was hospitalized with anemia requiring transfusion developed interstitial pneumonia 10 days after beginning lansoprazole 30 mg/day for gastric ulcer. Concomitant medications included sodium alginate, cefotiam, ceftazidime, and cefozopran. Lansoprazole was stopped and steroid therapy was started. The patient died five days later from interstitial pneumonia. The reporter stated that lansoprazole could not be excluded because of the temporal association, the absence of other known etiologies, and the existence of reports of similar cases.
- An 80 y/o female (THQ2000A01404) experienced collagenous colitis with diarrhea several weeks after treatment with lansoprazole for esophagitis. A dechallenge was positive. The patient died from pulmonary embolism (PE) due to prolonged bed confinement; the reporter indicated that this was accelerated by collagenous colitis.
- A 75 y/o female (TAP1999Q00604) taking lisinopril (ACE inhibitor) developed myelodysplastic syndrome ("pre-leukemia") and refractory anemia after 15 months of daily treatment with lansoprazole 15 mg for Barrett's esophagitis. She was instructed to stop lansoprazole and lisinopril, but the patient continued taking lansoprazole for another 2½ months due to severe reflux symptoms and then discontinued. She refused chemotherapy and was treated with transfusions; her myelodysplastic syndrome progressed and she died from sepsis a month after stopping lansoprazole. The oncologist and the primary care physician considered lansoprazole to be possibly or probably related to the dyscrasia; the gastroenterologist was unable to identify any causal relationship.
- A 72 y/o male (THQ2003A01376) was treated with lansoprazole for unspecified upper GI symptoms. He had ischemic heart, peripheral vascular disease, and a history of erythema multiforme (EM) prior to lansoprazole treatment. Concomitant medications were clopidogrel, diltiazem, simvastatin, and thiamine. A week later, he developed a rash which progressed to EM and toxic epidermal necrolysis. Lansoprazole was discontinued; he was treated with IV fluids and immunoglobulin. Two days later he developed rigors, left ventricular failure, and respiratory arrest; he was intubated, and given antibiotics. Except for the sacral pressure area, the patient's skin rapidly re-epithelized with no further blistering or detachment. He became oliguric due to sepsis and hypovolemia, and died two weeks later from multi-organ failure.
- A 71 y/o male (TCI2004A02334) with past history of hepatitis (30 years prior) and possible alcoholism was treated with lansoprazole for recurrent duodenal ulcer (he had been treated with lansoprazole 30 mg for 1 week two years prior). Fifteen days later, he presented with

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anorexia, malaise, and jaundice and was hospitalized for hepatitis. Lansoprazole was discontinued; hepatic failure was diagnosed 5 days later. Other hepatic-related diagnoses were excluded; therefore, the event was suspected to be due to lansoprazole. About 4 weeks later, stool culture yielded *Aeromonas caviae* and urine culture was positive for *Pseudomonas aeruginosa*; liver biopsy was indicative of acute hepatitis. He died one week later, with death attributed to liver failure. No autopsy was performed. In the reporter's opinion, drug-induced hepatitis was the most likely the cause of the liver failure, with a possible or probable relationship to lansoprazole because of the temporal association, although a viral etiology could not be definitively excluded.

- A 69 y/o male (THQ2003A01262) with a known allergy to proton pump inhibitors including lansoprazole, received lansoprazole for post-operative gastritis in an intensive care unit. No concomitant medications were reported. He developed an allergic reaction that was treated with unspecified medication. He subsequently developed SJS and was treated with immunoglobulin for 5 days, but developed multi-organ failure and died. There was no autopsy; the probable cause of death was reported as SJS and cardiac arrest. This report was received from the Medicines and Healthcare Products Regulatory Agency.
- A 51 y/o male (TCI2000A02430) developed fever (40°C/104°F) and was found to have decreased white blood cell count 5 weeks after lansoprazole therapy for bleeding gastric ulcer. Blood culture was positive for *Klebsiella*, pneumococcus, and *E. coli*. His condition deteriorated with disseminated intravascular coagulation, multi-organ failure, and died due to 'pneumorrhagia'. No significant infectious lesions in the lung or abdomen were identified on autopsy. Catheter infection or drug-induced agranulocytosis was suspected. The attending physician assessed a possible causal relationship between the events and lansoprazole.

In addition to the death cases discussed above, there were three cases with a reported outcome of fetal deaths and were discussed in section 7.1.14.

*Medical Officer Comments: A clear temporal relationship between the use of lansoprazole and death cannot be determined in most of the cases due to confounding factors such as underlying medical conditions, limited clinical information provided and/or concomitant use of other medication(s). It appears that other than reports of death due to anaphylaxis or allergic reaction, many of these patients were being treated for an underlying illness which was more likely the cause of death. The ten reports of death classified as Category 1 do not appear to show any trend or pattern in reporting.*

#### Blood and Hematologic Disorders (Postmarketing)

Of the overall 9,776 cases reporting AEs for lansoprazole, 369 (3.7%) cases (with 995 AE terms) had one or more events related to Hematologic disorders or related terms in the Investigations SOCs. Of these 369 cases, 14.6% (54) had an outcome of death compared to the overall lansoprazole treated population which was 2.2% (215/9,776). Overall, proportion of deaths from cases reporting AEs related to this organ system is 0.5% (54/9,776).

Most (78.3%, 289/369) cases were confounded with the use of concomitant medications which may have played a role in lansoprazole treated patients who experienced a hematologic AE. The medications more frequently reported as co-suspect and/or concomitant medication(s) were furosemide, levothyroxine, aspirin, and warfarin. The following six AEs were the most frequently reported and accounted for over half (51.2%) of all terms: anemia, thrombocytopenia, leukopenia, pancytopenia, agranulocytosis and platelet count decreased. Anemia has been reported for lansoprazole during clinical trials. The other five AEs have been reported during postmarketing and are currently listed on the lansoprazole prescription label. These six AE terms are also listed in the prescription label of another PPI, omeprazole, which is currently marketed for OTC use at a 20 mg dose.

### Cardiac Disorders

There were 225 cases with one or more events related to either the Cardiac disorders or Investigations SOC. These involved 258 cardiac related AEs and a total of 742 AEs across all SOCs. The proportion of deaths for cardiac related disorders was 10.2% (23/225) compared to the overall lansoprazole treated population which was 2.2% (215/9,776). Overall, proportion of deaths from cases reporting AEs related to this organ system is 0.2% (23/9,776).

The most frequently reported AE terms were palpitation (32.6%, 84/258) and tachycardia (10.5%, 27/258). Most cases (>80%) were non-serious. For cardiac related reports with a death outcome, the three most frequently reported events were myocardial infarction (6/27, 22.2%), cardiac arrest (6/27, 22.2%), and cardiac failure (5/27, 18.5%). The current lansoprazole prescription label includes the following events reported in less than 1% of patients in domestic trials: angina, arrhythmia, bradycardia, cerebrovascular accident/ cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, and vasodilation.

*Medical Officer Comments: The above data do not suggest any greater frequency in cardiac events with lansoprazole use compared to the overall population. Cardiovascular disease is currently the most common cause of death worldwide and accounts for ~30% of deaths worldwide, including nearly 40% in high-income countries and about 28% in low and middle income countries.<sup>12</sup>*

### Hepatobiliary Disorders

There were 287 reports (involving 410 AE terms) of patients out of the 9,776 cases reporting AEs for lansoprazole to either the Hepatobiliary SOC or the Investigation SOC. The five most frequently reported terms that accounts for over half (60.2%) of all the terms were: abnormal liver function test, hepatitis, increased ALT and AST, jaundice, and increased hepatic enzyme. The proportion of cases with a fatal outcome within these SOC was 12.9% (37/287) compared to

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<sup>12</sup> Harrison's Principles of Internal Medicine, 17th Ed. (2008) Online. Ch 218: Epidemiol of Cardiovasc Ds. (<http://online.statref.com/Document/Document.aspx?docId=1765&FxId=55&Scroll=1&Index=9&SessionId=E3DC2DPIHXDZOLET>) accessed on 1-7-09.

Clinical Review

Lolita A. Lopez, M.D.

NDA 22-327

Prevacid® 24HR (lansoprazole 15 mg) Delayed Release Capsule

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the proportion of death cases for the lansoprazole population overall (2.2%, 215/9,776). The proportion of deaths from cases reporting AEs related to this organ system is 0.3% (37/9776).

The data above reveal that in 73% (209/287) of cases associated with a hepatobiliary related AE, the patient was using concomitant medications. The drugs more frequently reported for the hepatobiliary related reports received for lansoprazole were furosemide, levothyroxine and aspirin; this suggest that concomitant medications may play a confounding role. Marked elevation of liver function tests, jaundice and liver disease (hepatitis) are AEs that have been previously identified with the use of other PPIs during clinical trials and/or postmarketing.

### Hip Fractures

An article published in the Journal of American Medical Association<sup>13</sup> concluded that long-term (>1 year) PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture. The AEs involving hip fracture during postmarketing will be discussed below.

There were two reports involving hip fracture and one involving a femoral neck fracture. All three cases were medically confirmed and were reported as unrelated to lansoprazole.

- A 77 y/o female experienced a non-traumatic hip fracture after approximately 3 months on lansoprazole therapy. Concomitant medications included Norvasc® (amlodipine) and Fosamax® (alendronate sodium). The reporter attributed the fracture to long standing osteoporosis and considered it unrelated to lansoprazole.
- A 91 y/o male with a hip prosthesis had a fracture and required replacement of the prosthesis after an unknown duration of lansoprazole treatment. Concurrent diseases/concomitant medications were not identified. The reporter considered the event unrelated to lansoprazole.
- A 78 y/o female on multi-drug therapy was hospitalized for a recurrence of pneumonia after 6 weeks on lansoprazole. While hospitalized, she experienced a bladder infection, blood in her stools, and dehydration, and was noted to have a hip fracture that required surgical placement of four stints. The reporter considered the event unrelated to lansoprazole.

*Medical Officer Comments: It should be noted that all three cases of hip fractures were in the elderly (>77 y/o), and in the two cases where duration of use was known, the use was at least 6 weeks. Due to the very small number of cases, it is not possible to establish that there is any risk attributable to lansoprazole treatment with regards to hip fractures from postmarketing. In addition, the proposed treatment course for the OTC use of lansoprazole is much shorter and less frequent use (14 days, and not more frequent than every 4 months (i.e., 3x/year).*

### Drug Interaction

There were a total of 162 reports with associated 485 AE terms received for drug interaction overall. Most cases (72.8%, 118) were non-serious, although 26.5% (43) were serious (non-fatal) cases, and one case (0.6%) had a fatal outcome. The most commonly reported AE term for

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13 Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006;296(24):2947-2953. TAP-07-900031

the cases retrieved was drug interaction (32.6%, 158/485), followed by nausea (2.9%, 14/485), and diarrhea (2.7%, 13/485). For serious cases involving 144 AE terms, the most commonly reported was convulsion (7/144, 4.9%), followed by diarrhea, condition aggravated, headache and weight decreased (each AE term at 2.1%, 3/144).

Of the 37/43 serious cases (cases associated with serious AE), the interacting drugs were co-suspect medications and in six cases, the interacting drug was captured as a concomitant medication. The drugs reported as interacting with lansoprazole at a frequency rate of  $\geq 2$  events for the 43 serious cases were phenytoin 7 (10%), warfarin 6 (8.6%), carbamazepine 4 (5.7%), and (2, 2.9% for each) albuterol, clarithromycin, levothyroxine, phenobarbital, salmeterol and montelukast sodium.

*Medical Officer Comments: The most commonly reported drugs for suspected interaction reported in postmarketing were phenytoin and warfarin. Lansoprazole is metabolized through the cytochrome P450 system. The prescription label states in healthy subjects, lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system (warfarin and phenytoin included). Neither the PK of warfarin enantiomers nor prothrombin time (PT) were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and PT in patients receiving PPIs; this may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. This warning is appropriately addressed in the proposed OTC label; the consumer is directed to ask a doctor if taking warfarin. There were other medications identified during postmarketing for drug interaction cases; however, the number of cases is small and the relationship to lansoprazole is uncertain. Therefore, this does not warrant any changes in the label.*

### Pneumonia

There were 32 cases with one or more terms pertaining to the PTs of interest for pneumonia. These cases involved 110 AE terms from all SOCs and 32 terms related specifically to pneumonia. The most frequently reported term was pneumonia (72%, 23/32), followed by pneumonia aspiration (9.4%, 3/32). The following were reported at a frequency of one: bronchopneumonia, pneumocystis jiroveci pneumonia, chlamydial pneumonia, cryptogenic organizing pneumonia, eosinophilic pneumonia, and pneumonitis.

In order to identify all cases associated with the term pneumonia, reports associated with the preferred term interstitial lung disease were further evaluated. A total of 14 cases were identified reporting this term: 1 non-serious case, 4 serious cases, and 9 cases associated with an outcome of death (previously discussed). When provided, the mean age of patients with an outcome of death was 78 years; an age group known to be predisposed to pneumonia and associated comorbidities. Of the four serious cases, reporter causality for the event was provided as "not related" in two cases, the other two medically confirmed cases are described below:

- TC12003A02799: An 83 y/o male with preexisting bacterial pneumonia was on IV antibiotics. He was started on omeprazole injection for 3 days followed by lansoprazole for

14 days. On the ninth day of lansoprazole use, the patient developed interstitial pneumonia. Involvement of both PPIs was reported likely. Pneumonia remained unchanged five days after discontinuation of lansoprazole. Discontinuation of arbekacin sulfate (a medication that had been used to treat the bacterial pneumonia) resulted in an improvement of symptoms.

- LTI2005A00155: A 60 y/o female took lansoprazole for several months. An unspecified time later, she was hospitalized for dyspnea and cutaneous lesions thought to be eczema. Lansoprazole was stopped approximately six weeks later, and the lesions improved. CT scan suggested bronchiolitis obliterans. Further information received indicated the patient's diagnosis was antisynthetase syndrome<sup>14</sup> (a chronic immune disease of unknown etiology) with interstitial pneumonitis. The patient improved with corticosteroids, and the skin reaction disappeared. This report was received from the French Medicine Agency.

On December 16, 2004, Health Canada requested an analysis regarding lansoprazole use and community acquired pneumonia (CAP). This analysis consisted of a literature review of epidemiology for CAP and a thorough review of TAP's safety database for lansoprazole. The results of this analysis were consistent with the data presented above. It should be noted that the reported annual incidences of invasive pneumococcal disease among persons  $\geq 65$  y/o in North America and Europe range from 25 to 90 cases per 100,000 persons. The data presented above reveal that the post marketing rate of pneumonia associated with lansoprazole use was 32 cases in an exposure of over 455 million (or 7 per 100 million), a much lower than the pneumococcal pneumonia rate in a 65 y/o population.

*Medical Officer Comments: From the postmarketing database, there were no new or unexpected findings revealed from the analysis of the safety profile for lansoprazole. As in the case from clinical efficacy trials previously conducted, the majority of reported events from postmarketing were not serious, mild, and self-limiting. The most frequent events were related to the Gastrointestinal SOC (diarrhea, nausea and abdominal pain) or drug ineffective.*

*It should be noted that reports from postmarketing are difficult to interpret; the main utility of these reports is that they can form a basis to identify signals of AEs associated with the drug. Due to the nature of most of the reports, it is difficult to assess causality to lansoprazole for the following reasons: insufficient information on timing, history, dechallenge, rechallenge; confounding factors such as the presence of an underlying medical illness or co-administration of multiple medications, or the presence of naturally occurring events (background rates) in the general population. In addition, with any spontaneous reporting, the proportion of cases to actual events is unknown and underreporting must also be considered.*

*Given the number of years that lansoprazole has been on the market and the estimated extensive population exposure, the data provided in the postmarketing surveillance did not present any*

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14 Anti-synthetase syndrome comprises the association of an inflammatory myopathy (polymyositis, dermatomyositis), interstitial pneumonitis, skin lesions characteristic of "mechanics hands", Raynaud's phenomena, inflammatory polyarthritis and, at the biological level, antinuclear antibodies known as anti-synthetases. (<http://www.ncbi.nlm.nih.gov/pubmed/12161705>)

*safety signal to suggest that lansoprazole would be unsafe for marketing in an OTC setting in adults ≥ 18 years of age for a duration of 2 weeks use.*

### Summary of Safety Data from the FDA's SRS and AERS Databases

The drug master file from each of the two FDA databases Spontaneous Reporting System (SRS) and Adverse Events Reporting System (AERS) were queried for all case reports for which a lansoprazole containing product was recorded as a suspect agent (SRS database) or the primary, secondary suspect or interacting agent (AERS database). A total of 4,704 cases were identified with 17,715 associated AE terms through June 30, 2007. Forty percent (40%; 1,882/4,704) of these cases were not serious; 44.9% (2,112/4,704) were serious; and 8.4% (394/4,704) involved reports of a death and 6.7% (316/4,704) had no outcome information. Among serious cases and deaths, the majority were in patients >18 y/o. More than half (60.5%) of the total reports were from health professionals, 23.6% were from consumers. There were numerous variations in reporting rates across the age groups without any consistent pattern. The AERS database contributed 82% of the reports and the SRS database, 18%. The total U.S. exposure to lansoprazole for the period covered by this report is estimated to be \_\_\_\_\_ Five SOCs accounted for 55.7% of all the reported AE terms:

- Gastrointestinal disorders (15.9%; 2,809/17,715)
- General disorders and administration site conditions (12.2%; 2,158/17,715)
- Investigations (10.3%; 1,828/17,715)
- Nervous system disorders (9.2%; 1,634/17,715)
- Skin and subcutaneous tissue disorders (8.2%; 1,444/17,715)

Of the 17,715 associated AE terms, the most commonly reported (reporting rates ≥1%) were: diarrhea (2.5%, 435), condition aggravated (1.7%, 300), nausea (1.5%, 262), abdominal pain (1.3%, 227), pyrexia (1.3%, 223), drug interaction (1.2%, 212), and headache (1%, 169).

With regard to *serious* cases, there were 2,112 reports with 9,977 associated AE terms. Five SOCs accounted for 55.3% of all the reported terms:

- Gastrointestinal disorders (14.4%; 1,437/9,977)
- General disorders and administration site conditions (11.4%; 1,139/9,977)
- Investigations (12%; 1,202/9,977)
- Nervous system disorders (8.8%; 873/9,977)
- Skin and subcutaneous tissue disorders (8.6%; 863/9,977)

Of the 9,977 associated AE terms for *serious* cases, the most frequently reported AE terms (reporting rates ≥1%) were: diarrhea (1.9%, 190), pyrexia (1.7%, 171), nausea (1.3%, 125), condition aggravated (1.1%, 113), drug interaction (1.1%, 106), vomiting (1%, 104), and thrombocytopenia (1%, 98). See table below.

b(4)

**Table 15: Most Frequent AE Terms for Lansoprazole by Seriousness ( $\geq 0.5\%$ ) N (%)<sup>a</sup>  
 (SRS/AERS)**

SOC Abbr <sup>b</sup>	MedDRA Preferred Term	Not serious	Serious	Death	No outcome data	Overall total
Gastr	Diarrhoea	<b>188 (4.0)</b>	190 (1.9)	15 (0.6)	<b>42 (5.5)</b>	435 (2.5)
Genrl	Condition aggravated	<b>146 (3.1)</b>	113 (1.1)	28 (1.2)	13 (1.7)	300 (1.7)
Gastr	Nausea	<b>114 (2.4)</b>	125 (1.3)	8 (0.3)	<b>15 (2.0)</b>	262 (1.5)
Gastr	Abdominal pain	<b>114 (2.4)</b>	90 (0.9)	6 (0.3)	<b>17 (2.2)</b>	227 (1.3)
Genrl	Pyrexia	20 (0.4)	<b>171 (1.7)</b>	31 (1.3)	1 (0.1)	223 (1.3)
Genrl	Drug interaction	<b>81 (1.7)</b>	106 (1.1)	7 (0.3)	<b>18 (2.4)</b>	212 (1.2)
Nerv	Headache	<b>91 (2.0)</b>	53 (0.5)	7 (0.3)	<b>18 (2.4)</b>	169 (1.0)
Genrl	Asthenia	<b>59 (1.3)</b>	91 (0.9)	10 (0.4)	6 (0.8)	166 (0.9)
Gastr	Vomiting	39 (0.8)	<b>104 (1.0)</b>	10 (0.4)	10 (1.3)	163 (0.9)
Nerv	Dizziness	<b>71 (1.5)</b>	70 (0.7)	2 (0.1)	<b>19 (2.5)</b>	162 (0.9)
Resp	Dyspnoea	<b>52 (1.1)</b>	87 (0.9)	13 (0.6)	4 (0.5)	156 (0.9)
Genrl	Drug ineffective	<b>68 (1.5)</b>	55 (0.6)	4 (0.2)	<b>20 (2.6)</b>	147 (0.8)
Blood	Thrombocytopenia	8 (0.2)	<b>98 (1.0)</b>	<b>27 (1.2)</b>	2 (0.3)	135 (0.8)
Skin	Pruritus	<b>49 (1.1)</b>	73 (0.7)		9 (1.2)	131 (0.7)
Skin	Dermatitis	<b>75 (1.6)</b>	42 (0.4)	2 (0.1)	4 (0.5)	123 (0.7)
Inv	Liver function test abnormal	23 (0.5)	<b>77 (0.8)</b>	11 (0.5)	3 (0.4)	114 (0.6)
Genrl	Malaise	15 (0.3)	<b>77 (0.8)</b>	9 (0.4)	1 (0.1)	102 (0.6)
Skin	Urticaria	29 (0.6)	64 (0.6)	1 (0.0)	4 (0.5)	98 (0.6)
Genrl	Chest pain	<b>36 (0.8)</b>	50 (0.5)	8 (0.3)	3 (0.4)	97 (0.5)
Psych	Insomnia	<b>63 (1.4)</b>	29 (0.3)	1 (0.0)	4 (0.5)	97 (0.5)
Eye	Vision blurred	26 (0.6)	28 (0.3)		<b>41 (5.4)</b>	95 (0.5)
Hepat	Jaundice	8 (0.2)	<b>74 (0.7)</b>	13 (0.6)		95 (0.5)
Psych	Confusional state	18 (0.4)	<b>69 (0.7)</b>	4 (0.2)	3 (0.4)	94 (0.5)
Gastr	Abdominal pain upper	18 (0.4)	57 (0.6)	5 (0.2)	9 (1.2)	89 (0.5)
Genrl	Fatigue	25 (0.5)	54 (0.5)	4 (0.2)	5 (0.7)	88 (0.5)
Inv	Weight decreased	24 (0.5)	57 (0.6)		7 (0.9)	88 (0.5)
Blood	Leukopenia	12 (0.3)	54 (0.5)	<b>19 (0.8)</b>	2 (0.3)	87 (0.5)
Metab	Anorexia	17 (0.4)	56 (0.6)	12 (0.5)		85 (0.5)
Inv	Alanine aminotransferase increased	15 (0.3)	<b>55 (0.6)</b>	10 (0.4)	1 (0.1)	81 (0.5)
Genrl	Oedema peripheral	<b>31 (0.7)</b>	47 (0.5)	1 (0.0)	1 (0.1)	80 (0.5)
Genrl	Pain	<b>42 (0.9)</b>	26 (0.3)	7 (0.3)	5 (0.7)	80 (0.5)
Infec	Pneumonia	3 (0.1)	40 (0.4)	<b>36 (1.5)</b>	1 (0.1)	80 (0.5)
	<b>Total terms<sup>c</sup> (col %)</b>	4654 (100)	9977 (100)	2325 (100)	759 (100)	17715 (100)
	<b>Total terms<sup>a</sup> (row %)</b>	4654 (26.3)	9977 (56.3)	2325 (13.1)	759 (4.3)	17715 (100)
	<b>Total cases<sup>a</sup> (row %)</b>	1882 (40.0)	2112 (44.9)	394 (8.4)	316 (6.7)	4704 (100)

<sup>a</sup> Unless otherwise indicated, the percent basis is the total number of preferred terms in each seriousness category. Terms with >10 events and a relative reporting rate >20% higher than the corresponding overall rate are highlighted in bold.

<sup>b</sup> System Organ Class Contents.

<sup>c</sup> The totals are those for the entire dataset, not just the data displayed in the table.

Sponsor's Table Module 5.3.5.3 Appendix 3 to ISS, p.21

From the available data in the reports, especially those that involved cases reported as serious, it is difficult to discern whether the outcome is attributed to the lansoprazole or to an underlying condition for which lansoprazole was administered, or underlying conditions for which the patients were being treated.

There were 3 reports of hip fracture and 2 of femoral neck fracture. All were females; 4 of the cases were categorized as serious (most likely due to requirement of hospitalization), 1 was reported death. Four of the five had age data and the ages ranged from 77 to 90 years, and lansoprazole usage was at least 4 weeks duration prior to diagnosis of hip fracture. All of the patients were on concomitant medications; three patients had pneumonia or bronchitis. There was limited information provided on all the cases reported.

#### Deaths (SRS/AERS Data)

There were 394 (8.4%) reported deaths with 2,325 associated AE terms which were distributed across a broad range of SOCs. The five SOCs with the highest reporting rates that accounted for 1,099 terms (47.3%) were:

- Investigations (12.6%; 292/2,325)
- Respiratory, thoracic and mediastinal disorders (9.2%; 213/2,325)
- General disorders and administration site conditions (9.1%; 211/2,325)
- Gastrointestinal disorders (8.5%; 198/2,325)
- Blood and lymphatic system disorders (8%; 185/2,325)

The 10 most frequently reported AE terms with reporting rates >1% among the reports of death were: sepsis (1.7%, 40), pneumonia (1.5%, 36), pyrexia (1.3%, 31), hepatic failure (1.2%, 29), condition aggravated 1.2% (28/2,325), thrombocytopenia 1.2% (27/2,325), multi-organ failure (1.2%, 27), disseminated intravascular coagulation (1.1%, 26), gastrointestinal hemorrhage (1.1%, 26), and renal failure (1.1%, 25) (Table 16).

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Table 16: Most Frequent AEs for Reports of Death (≥0.6%) N (%)<sup>a</sup> (SRS/AERS)

SOC Abbr <sup>b</sup>	MedDRA Preferred Term	≤11	12-17	18-65	>65	No age data	Overall total
Infec	Sepsis			17 (2.4)	22 (1.5)	1 (0.8)	40 (1.7)
Infec	Pneumonia			5 (0.7)	29 (2.0)	2 (1.6)	36 (1.5)
Genrl	Pyrexia			9 (1.3)	20 (1.4)	2 (1.6)	31 (1.3)
Hepat	Hepatic failure			8 (1.1)	20 (1.4)	1 (0.8)	29 (1.2)
Genrl	Condition aggravated			6 (0.8)	20 (1.4)	2 (1.6)	28 (1.2)
Blood	Thrombocytopenia			5 (0.7)	19 (1.3)	3 (2.4)	27 (1.2)
Genrl	Multi-organ failure			9 (1.3)	17 (1.1)	1 (0.8)	27 (1.2)
Blood	Disseminated intravascular coagulation			14 (2.0)	11 (0.7)	1 (0.8)	26 (1.1)
Gastr	Gastrointestinal haemorrhage			2 (0.3)	23 (1.6)	1 (0.8)	26 (1.1)
Renal	Renal failure			7 (1.0)	16 (1.1)	2 (1.6)	25 (1.1)
Neopl	Mesothelioma				19 (1.3)	4 (3.2)	23 (1.0)
Card	Myocardial infarction			4 (0.6)	18 (1.2)		22 (0.9)
Inv	Blood pressure decreased			7 (1.0)	14 (0.9)		21 (0.9)
Nerv	Depressed level of consciousness			10 (1.4)	10 (0.7)	1 (0.8)	21 (0.9)
Card	Cardiac failure			4 (0.6)	15 (1.0)	1 (0.8)	20 (0.9)
Blood	Leukopenia			1 (0.1)	18 (1.2)		19 (0.8)
Blood	Pancytopenia			4 (0.6)	15 (1.0)		19 (0.8)
Card	Cardiac arrest			9 (1.3)	10 (0.7)		19 (0.8)
Resp	Pulmonary oedema			3 (0.4)	14 (0.9)		17 (0.7)
Skin	Toxic epidermal necrolysis			7 (1.0)	10 (0.7)		17 (0.7)
Vasc	Shock			5 (0.7)	12 (0.8)		17 (0.7)
Blood	Agranulocytosis			10 (1.4)	6 (0.4)		16 (0.7)
Gastr	Gastric ulcer			5 (0.7)	10 (0.7)	1 (0.8)	16 (0.7)
Hepat	Hepatic function abnormal			7 (1.0)	7 (0.5)	2 (1.6)	16 (0.7)
Resp	Respiratory failure			1 (0.1)	14 (0.9)	1 (0.8)	16 (0.7)
Gastr	Diarrhoea			6 (0.8)	9 (0.6)		15 (0.6)
Hepat	Hepatocellular damage			1 (0.1)	12 (0.8)	2 (1.6)	15 (0.6)
Resp	Interstitial lung disease			3 (0.4)	11 (0.7)	1 (0.8)	15 (0.6)
Surg	Haemodialysis			6 (0.8)	9 (0.6)		15 (0.6)
Inv	Haemoglobin decreased			6 (0.8)	7 (0.5)	1 (0.8)	14 (0.6)
Skin	Stevens-Johnson syndrome			6 (0.8)	8 (0.5)		14 (0.6)
Hepat	Jaundice			4 (0.6)	7 (0.5)	2 (1.6)	13 (0.6)
Inj&P	Overdose				13 (0.9)		13 (0.6)
Resp	Dyspnoea			7 (1.0)	6 (0.4)		13 (0.6)
Resp	Respiratory disorder			1 (0.1)	12 (0.8)		13 (0.6)
	<b>Total terms<sup>c</sup> (col %)</b>	6 (100)	0	713 (100)	1481 (100)	125 (100)	2325 (100)
	<b>Total terms<sup>c</sup> (row %)</b>	6 (0.3)	0 (0.0)	713 (30.7)	1481 (63.7)	125 (5.4)	2325 (100)
	<b>Total cases<sup>c</sup> (row %)</b>	2 (0.5)	0 (0.0)	106 (26.9)	249 (63.2)	37 (9.4)	394 (100)

<sup>a</sup> Unless otherwise indicated, the percent basis is the total number of preferred terms in each age group. Terms with >10 events and a relative reporting rate >20% higher than the corresponding overall rate are highlighted in bold.

<sup>c</sup> The totals are those for the entire dataset, not just the data displayed in the table.

*Sponsor's Table, Module 5.3.5.3 Appendix 3 to ISS p.30*

*Medical Officer Comments: For the reported death cases, it is to be noted that all or some of the most commonly reported AEs may occur in a patient with sepsis and/or critically ill. It is not clear from the available data if the association with lansoprazole was a result of ulcer prophylaxis in a critically ill patient. Pneumonia is the second most frequently reported adverse event (Table 16) and the age distribution was skewed to older age ranges. For the reported cases of death, 63.7% occurred in elderly patients (≥ 65 years old) compared to 26.9% in patients 18 to 65 years old. In general, pneumonia is one of the five leading causes of death in the elderly. It is possible that elderly patients were being treated due to an underlying pneumonia or respiratory illness. It is also possible that more elderly patients have serious underlying disease(s) associated with more complications leading to death. There was no single organ system or AE term that was consistently associated with the 394 reported death cases. There were no new adverse events identified that occurred at a significant frequency in these reports.*

*The FDA/SRS database did not reveal any new serious, unusual or significant safety concerns associated with the use of lansoprazole for a particular organ system at the current recommended dose and duration of use. In general, the types of adverse events from this database, such as diarrhea, nausea, abdominal pain, and headache are similar to those previously reported with the use of this drug both during clinical trials and from the sponsor's database. It is to be noted causality cannot be determined in most of the cases due to lack of more specific clinical information. In addition, reports regarding the same case may sometimes be received from several different sources at different times (duplicate reports).*

#### **Summary of Safety Data from the WHO Vigibase Drug Safety Database**

The sponsor obtained reports of AEs associated with lansoprazole as a suspect medication from the World Health Organization (WHO) drug safety database maintained in Uppsala, Sweden. The reports were segregated by country of origin; those originating outside the U.S. (exUS) were the focus of the report. The first report identified for lansoprazole in the database was dated October 29, 1993 and the most recent was July 31, 2008.

There were a total of 6,609 cases involving 13,571 MedDRA AE terms reported for lansoprazole in the WHO database. Two-thirds of these cases (70%; 4,606) involving 8,165 (60%) AE terms were reported from exUS and one-third of the cases (30%; 2,003) involving 5,406 (40%) AE terms were US cases. The exUS cases will be the primary focus of this review. Cases of U.S. origin were discussed in a separate section (in the FDA's SRS and AERS databases).

Table 17 presents the most frequently reported AE terms in descending order of overall frequency for the foreign and U.S. reports.

**Table 17: Most Frequently Reported AEs (≥ 0.6%): exUS and US Reports N (%)<sup>a</sup>  
 (WHO Data)**

SOC Abbreviation	MedDRA Preferred term	exUS	US	Overall Total
Gastr	Diarrhoea	533 (6.5)	215 (4.0)	748 (5.5)
Nerv	Headache	368 (4.5)	77 (1.4)	445 (3.3)
Skin	Rash	304 (3.7)	43 (0.8)	347 (2.6)
Skin	Pruritus	280 (3.4)	48 (0.9)	328 (2.4)
Gastr	Nausea	206 (2.5)	120 (2.2)	326 (2.4)
Gastr	Abdominal pain	173 (2.1)	118 (2.2)	291 (2.1)
Nerv	Dizziness	187 (2.3)	92 (1.7)	279 (2.1)
Musc	Arthralgia	218 (2.7)	35 (0.6)	253 (1.9)
Skin	Urticaria	195 (2.4)	45 (0.8)	240 (1.8)
Musc	Myalgia	144 (1.8)	29 (0.5)	173 (1.3)
Genrl	Condition aggravated	16 (0.2)	151 (2.8)	167 (1.2)
Gastr	Vomiting	107 (1.3)	55 (1.0)	162 (1.2)
Resp	Dyspnoea	86 (1.1)	68 (1.3)	154 (1.1)
Psych	Depression	115 (1.4)	25 (0.5)	140 (1.0)
Genrl	Fatigue	99 (1.2)	31 (0.6)	130 (1.0)
Eye	Vision blurred	67 (0.8)	50 (0.9)	117 (0.9)
Gastr	Dry mouth	80 (1.0)	33 (0.6)	113 (0.8)
Genrl	Malaise	91 (1.1)	14 (0.3)	105 (0.8)
Nerv	Paraesthesia	76 (0.9)	29 (0.5)	105 (0.8)
Genrl	Chest pain	43 (0.5)	60 (1.1)	103 (0.8)
Skin	Rash erythematous	95 (1.2)	8 (0.1)	103 (0.8)
Blood	Thrombocytopenia	68 (0.8)	32 (0.6)	100 (0.7)
Genrl	Asthenia	33 (0.4)	66 (1.2)	99 (0.7)
Psych	Confusional state	60 (0.7)	38 (0.7)	98 (0.7)
Genrl	Oedema	83 (1.0)	13 (0.2)	96 (0.7)
Genrl	Pyrexia	61 (0.7)	32 (0.6)	93 (0.7)
Gastr	Flatulence	52 (0.6)	40 (0.7)	92 (0.7)
Hepat	Hepatic function abnormal	80 (1.0)	12 (0.2)	92 (0.7)
Psych	Insomnia	39 (0.5)	52 (1.0)	91 (0.7)
Genrl	Pain	47 (0.6)	40 (0.7)	87 (0.6)
Skin	Rash maculo-papular	77 (0.9)	10 (0.2)	87 (0.6)
Gastr	Dyspepsia	43 (0.5)	37 (0.7)	80 (0.6)
Hepat	Jaundice	66 (0.8)	14 (0.3)	80 (0.6)
Gastr	Constipation	55 (0.7)	22 (0.4)	77 (0.6)
Genrl	Face oedema	57 (0.7)	18 (0.3)	75 (0.6)
	<b>Total terms<sup>b</sup> (row %)</b>	<b>8165 (60.2)</b>	<b>5406 (39.8)</b>	<b>13571 (100)</b>
	<b>Total cases (row %)</b>	<b>4606 (69.7)</b>	<b>2003 (30.3)</b>	<b>6609 (100)</b>

<sup>a</sup> Unless otherwise indicated, the percent basis is the total number of case reports for each geographic category.

<sup>b</sup> Total of all terms not just those in the table.

Sponsor's Table, Appendix 6 to ISS: WHO Database p.14

Of the 4,606 exUS cases, 95% (4,378) were categorized as nonserious, 4% (185) were serious, 0.9% (42) were death cases and 1 case had no data. It should be noted that for reports of U.S. origin, 11% (222/2,003) were categorized as serious, but this probably reflects, in part, a WHO coding error. The U.S. cases with "Other" as an outcome were identified in the WHO database as serious; this comprised 4% (80/2,003) of the total U.S. cases.

Most (92.4%; 4,253/4,606) of the exUS reports were in adults (≥ 18 years of age) and pediatric cases (≤ 17 years) accounted for 0.9% (40/4606); there were no age data reported in 6.8% (313/4,606) of reported terms. Overall, there was no clustering or consistent pattern of AEs across the age groups. A 'General Practitioner' was listed the leading source with 12% (555) and a 'Physician' was the next leading source with 8.7% (402); there was no source information

for 59.3% (2,733) of cases. Four countries accounted for 77.5% (3,571) of the total cases: the United Kingdom 57.8% (2,663), France 10.3% (476), Australia 5% (232) and Germany 4.3% (200). The following four SOCs accounted for 61% (4,987/8,165) of the total AE terms: Gastrointestinal disorders 20.8%, Skin and subcutaneous tissue disorders 18.8%, Nervous system disorders 2.2%, General disorders and administration site conditions 9.4%. The most frequently reported AE terms (>2%) for ex-US cases that accounted for 30.2% (2464/8165) of all reported terms were: diarrhea (6.5%), headache (4.5%), rash (3.7%), pruritus (3.4%), arthralgia (2.7%), nausea (2.5%), urticaria (2.4%), dizziness (2.3%), and abdominal pain (2.1%).

With regard to 185 serious reports involving 348 AE terms, the following four SOCs had the highest frequencies of reports and accounted for 55.5% (193/348) of the AE terms: Skin and subcutaneous tissue disorders 18.7%, Gastrointestinal disorders 15.5%, Blood and lymphatic system disorders 12.6%, and Investigations 8.6%. With respect to individual serious AE terms, the following had reporting rates  $\geq 2\%$  and accounts for 30.5% (106/348) of all reported terms:

- |                       |                |                     |               |
|-----------------------|----------------|---------------------|---------------|
| • Diarrhea            | (4.3%, 15/348) | • Confusional state | (2.3%, 8/348) |
| • Colitis             | (4.0%, 14/348) | • Urticaria         | (2.3%, 8/348) |
| • Hyponatraemia       | (3.4%, 12/348) | • Neutropenia       | (2%, 7/348)   |
| • Thrombocytopenia    | (3.2%, 11/348) | • Pruritus          | (2%, 7/348)   |
| • Renal failure acute | (2.6%, 9/348)  | • Rash              | (2%, 7/348)   |
| • Hepatitis           | (2.3%, 8/348)  |                     |               |

#### Deaths (WHO Data)

There were 42 deaths with 87 associated AE terms reported; this comprises 0.9% (42/4606) of all reported exUS cases. Most (62%, 26/42) of the reports were in the geriatric age range; there were no reports of death in the pediatric age ranges. Four SOCs had relative rates >10% of all reported terms for the cases of death accounting for 53% (46/87) of the total terms: Blood and lymphatic system disorders 18.4%, Skin and subcutaneous tissue disorders 12.6%, General disorders and administration site conditions 11.5%, and Hepatobiliary disorders 10.3%. The most frequently reported ( $\geq 3$  reports) adverse event terms were toxic epidermal necrolysis (5.7%, 5/87), thrombocytopenia (4.6%, 4/87), death (4.6%, 4/87) and sudden death (3.4%, 3/87). No other single AE term had more than two reports.

*Medical Officer Comments: The types of adverse events from the WHO database: diarrhea, nausea, abdominal pain and condition aggravated are similar to those previously reported adverse events with the use of lansoprazole both during clinical trials and postmarketing. This database did not reveal any new or unexpected safety findings with lansoprazole for OTC use.*

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

#### 7.2.1.1 Study type and design/patient enumeration

Below is a summary of the study design of the three clinical trials conducted for the indication of frequent heartburn.

**Table 16: Summary of Trials**

Study No.	Study objective, population	Planned/ Actual subjects	Treatment duration	Dosage	Type of control
<b>Controlled efficacy trials</b>					
PRSW-GN-301	Randomized, double-blind, placebo-controlled, parallel-group, multi-center study of efficacy/safety in frequent heartburn	576/564	2 weeks	lansoprazole 15 mg QD	Placebo control
PRSW-GN-302	Randomized, double-blind, placebo-controlled, parallel-group, multi-center study of efficacy/safety in frequent heartburn	576/570	2 weeks	lansoprazole 15 mg QD	Placebo control
PRSW-GN-305	Randomized, double-blind, placebo-controlled, parallel-group, multi-center study of efficacy/safety in frequent nighttime heartburn	864/852	2 weeks	lansoprazole 15 mg or 30 mg QD	Placebo control

#### 7.2.1.2 Demographics

The treatment groups appear to be generally well matched for demographic characteristics at baseline. Table 19 lists the demographic features by treatment.

**Table 19: Demographic Features by Treatment**

	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg
<b>Total subjects<sup>a</sup></b>	861	848	277
<b>Sex - N (%)</b>			
Male	320 (37.2)	295 (34.8)	94 (33.9)
Female	541 (62.8)	553 (65.2)	183 (66.1)
<b>Ethnicity - N (%)</b>			
Caucasian	609 (70.7)	587 (69.2)	191 (69.0)
Hispanic	117 (13.6)	123 (14.5)	35 (12.6)
Black	97 (11.3)	100 (11.8)	41 (14.8)
Asian	22 (2.6)	22 (2.6)	9 (3.2)
Other	16 (1.9)	16 (1.9)	1 (0.4)
<b>Age (yr) - N (%)</b>			
N	861	848	277
Mean - SD	48.0 - 14.2	47.7 - 13.6	48.8 - 14.1
Median	48.0	48.0	49.0
Range	18 - 90	18 - 86	18 - 85
< 40	238 (27.6)	239 (28.2)	67 (24.2)
40 - 65	518 (60.2)	505 (59.6)	172 (62.1)
≥ 65	105 (12.2)	104 (12.3)	38 (13.7)
<b>Height (inches)</b>			
N	861	847	277
Mean - SD	66.1 - 3.9	66.0 - 4.0	66.1 - 4.2
Median	66.0	65.0	65.0
Range	52 - 76	50 - 90	54 - 78
<b>Weight (lb)</b>			
N	861	846	277
Mean - SD	188.3 - 48.6	188.1 - 46.4	185.6 - 45.8
Median	181.0	182.0	183.0
Range	88 - 425	88 - 401	96 - 368
<100	3 (0.3)	4 (0.5)	1 (0.4)
100 - <150	169 (19.6)	165 (19.5)	56 (20.2)
150 - <200	406 (47.2)	381 (45.0)	126 (45.5)
200 - <250	190 (22.1)	209 (24.7)	71 (25.6)
250 - <300	65 (7.5)	67 (7.9)	19 (6.9)
≥300	28 (3.3)	20 (2.4)	4 (1.4)
<b>BMI (kg/m<sup>2</sup>)</b>			
N	861	845	277
Mean - SD	30.3 - 7.2	30.4 - 7.1	29.9 - 6.7
Median	28.7	29.5	29.1
Range	17 - 71	16 - 65	17 - 59

<sup>a</sup>Unless otherwise indicated, the number of subjects used to calculate the mean values is given at the top of the table as "N".

SD = standard deviation; BMI = body mass index

Sponsor's table CTD 2.7.4 p.21

*Medical Officer Comments: There was only one statistically significant difference detected between the 15 mg treatment group and the placebo group evident in the demographic data. The gender distribution in the Black, Asian and Other ethnic subgroup had 41.5% (56/135) males in the 15 mg group compared to 29% (40/138) in the placebo group. This is not expected to affect the safety profile for lansoprazole with regard to gender. The subject populations were otherwise comparable.*

#### 7.2.1.3. Extent of exposure (dose/duration)

Of the 1,986 subjects in the three controlled clinical trials; 1,138 subjects were treated and received at least one dose of lansoprazole (861 received lansoprazole 15 mg, 277 received

lansoprazole 30 mg) and 848 were treated with placebo. The proportion of subjects who discontinued regardless of the reason was similar for all the treatment groups. A summary of the total dose exposure for the major safety population of subjects with frequent heartburn is listed in Table 20. The study medication was taken once daily; the number of days is synonymous with the number of doses.

**Table 20: Overall Exposure during the Treatment Phase by Total Doses (Major Safety Population)**

Unadjusted Days - N (%)	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg
1	2 (0.2)	2 (0.2)	1 (0.4)
2	3 (0.3)	5 (0.6)	0 (0.0)
3	5 (0.6)	0 (0.0)	0 (0.0)
4	3 (0.3)	3 (0.4)	1 (0.4)
5	3 (0.3)	1 (0.1)	0 (0.0)
6	3 (0.3)	3 (0.4)	0 (0.0)
7	1 (0.1)	0 (0.0)	1 (0.4)
8	3 (0.3)	1 (0.1)	0 (0.0)
9	4 (0.5)	4 (0.5)	3 (1.1)
10	11 (1.3)	10 (1.2)	5 (1.8)
11	8 (0.9)	17 (2.0)	4 (1.4)
12	38 (4.4)	31 (3.7)	3 (1.1)
13	121 (14.1)	126 (14.9)	30 (10.8)
14	656 (76.2)	645 (76.1)	229 (82.7)
N	861	848	277
Mean (95% CI)	13.4 (13.3 - 13.5)	13.5 (13.4 - 13.6)	13.6 (13.4 - 13.8)
Median	14.0	14.0	14.0
Min-Max	1 - 14	1 - 14	1 - 14
The active treatments studies were all of 2 weeks duration.			
The percent basis is the number of subjects enrolled for a given treatment.			

All (1,138) subjects received an average of 13.45 doses of lansoprazole in the three studies. Most (76.2%) received 14 doses of lansoprazole 15 mg and approximately 5% of the subjects received ≤11 days of study treatment. There appears to be no significant differences in the mean number of days of exposure by treatment group.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Postmarketing safety data are discussed in section 7.1.17 and safety data from published literature are discussed in section 8.6 of this review.

Lansoprazole (Prevacid®) was first approved in the United States in May 1995. Worldwide, over 10,000 patients have been treated with prescription lansoprazole in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment (see prescription label). In December 2007, the estimated worldwide exposure with lansoprazole was over \_\_\_\_\_ with estimated U.S. sales of \_\_\_\_\_ prescriptions through June 2007.

b(4)

### 7.2.3 Adequacy of Overall Clinical Experience

Lansoprazole (Prevacid) has been proven safe and effective at various dosages (including 90 mg twice a day) and for various indications in the United States for over 13 years. Therefore, there is an adequate clinical experience with lansoprazole from prescription use.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There are no new animal studies nor in vitro testing submitted with this NDA.

### 7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing which included vital signs, physical exam, EKG, urinalysis, hematology, and chemistry were adequate for the studies conducted.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new information on metabolic, clearance and interaction was submitted with this NDA.

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This section is not applicable.

### 7.2.8 Assessment of Quality and Completeness of Data

A consult to the Division of Scientific Investigation was requested and the result of their evaluation was still pending at the time this review was written.

### 7.2.9 Additional Submissions, Including Safety Update

A 4-month Safety Update was submitted that provided summaries of postmarketing safety report from October 2007 to July 2008; medical literature review from January 2008 to July 2008; WHO Vigibase system through August 2008 (discussed in section 7.1.17); and the FDA's SRS/AERS databases current through June 2008 (this period covers the initial NDA submission and the incremental period of June 2007 to June 2008). No new clinical trials were completed by the sponsor during this time.

For the postmarketing safety update, there were 431 case reports with 778 AE terms reported for single ingredient lansoprazole from October 2007 to July 2008. Most (84.2%) reports (363/431) were classified as non-serious; 13.7% (59/431) were serious; and 2.1% (9/431) were death cases. The most common events were in the gastrointestinal (GI) disorders (31.2%), General disorders and administration site conditions (15%), and Skin and subcutaneous tissue disorders (8.4%). Of

the 778 AE terms, the most commonly reported ( $\geq 1\%$ ) overall were: drug ineffective (70, 9%); diarrhea (43, 5.5%); nausea (22; 2.8%); abdominal pain (19, 2.4%); constipation (19, 2.4%); vomiting (16, 2.1%); dizziness (15, 1.9%); insomnia (14, 1.8%); drug interaction (13, 1.7%); rash (12, 1.5%); abdominal pain upper (10; 1.3%); dyspnea (10, 1.3%); headache (10, 1.3%); flatulence (9, 1.2%); abdominal distension (9, 1.2%); and wrong technique in drug usage process injury (8, 1%).

Among the 163 AE terms (which could include both serious and non-serious terms) associated with serious cases, the most frequently reported were: drug interaction (10, 6.1%), cardiac tamponade (6, 3.7%); diarrhea (3, 1.8%); renal failure acute (3, 1.8%); and the following which occurred at a rate of 1.2% (2 events) vomiting, GERD, abdominal pain upper, constipation, urticaria, cutaneous lupus erythematosus, face swelling, erythema, Stevens-Johnson syndrome, rash, pyrexia, drug ineffective, tremor, syncope, dyspnea, suicidal ideation, insomnia, increased blood creatine phosphokinase, rhabdomyolysis, hip fracture, drug exposure during pregnancy, dehydration, visual disturbance, hemorrhage, neutropenia, and abortion spontaneous. Majority (80%, 8/10) of the drug interaction AE was derived from literature reports and contained limited information regarding patient history; of these, 7 were suspected drug interactions with warfarin. The six reports of cardiac tamponade were derived from two literature sources (Hata 2007 and Hata 2008); all cases had history of valve replacement or atrial septal defect and listed warfarin as a co-suspect medication. Most of the deaths reported in this safety update had documentation of confounding factors such as an underlying medical illness or concomitant use of multiple medications that may possibly have contributed to the outcome of death.

In general, the profiles of data and the percentage of non-serious, serious and death reports during postmarketing were similar to those of the initial reporting period. The safety profile for lansoprazole 15 mg in this 4-month safety update from the postmarketing, including FDA's SRS/AERS databases, and literature review, is consistent with the findings in the initial NDA submission. There were no new or unexpected safety issues identified in this 4-month safety update.

### **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

Diarrhea was the only drug-related adverse event experienced with the use of lansoprazole in both clinical efficacy trials for prescription and OTC use, as well as use from postmarketing. Lansoprazole has been marketed worldwide (including the United States) for over 13 years. The safety profile of lansoprazole is well-characterized; there should be no new unexpected safety issues if the 15 mg dosage strength is marketed for OTC use for a duration of 2 weeks in the United States.

## 7.4 General Methodology

### 7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

In clinical trials conducted for the OTC indication, all subjects exposed to at least one dose of study treatment from the three randomized, blinded, placebo controlled phase III trials were pooled to examine the incidence rate of AEs, SAEs and deaths by the affected body systems, type of underlying event, and suspected drug relatedness. Pooling of data for the controlled clinical studies was accomplished by summation of the events (numerator) and subjects (denominator) for the AE data. Descriptive statistics were used to express AE frequencies and were not formally compared between treatment groups for individual AEs.

For these clinical trials, the adverse event suspected to be related to the study drug during the treatment phase was diarrhea: lansoprazole 15 mg group, 0.6% (5/861); lansoprazole 30 mg, 0.7% (2/277) compared to placebo, 0.1% (1/848). The SOC with the most frequently reported AEs in the treatment phase for each treatment group was the gastrointestinal disorders.

In clinical trials previously conducted for lansoprazole for prescription use, over 10,000 patients have been treated worldwide with lansoprazole in Phase 2 or Phase 3 trials involving various dosages and durations of treatment. The following adverse events were reported by the treating physician to have a possible or probable relationship to the drug in 1% or more of lansoprazole-treated patients and occurred at a greater rate in lansoprazole-treated patients than placebo-treated patients: abdominal pain (2.1% vs. 1.2%), constipation (1% vs. 0.4%), diarrhea (3.8% vs. 2.3%) and nausea (1.3% vs. 1.2%). The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was also diarrhea.

Thus, diarrhea is an adverse event consistently reported among the clinical studies conducted for prescription and OTC indications.

### 7.4.2 Explorations for Predictive Factors

There were no explorations for predictive factors submitted with these applications.

### 7.4.3 Causality Determination

This section is not applicable.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The proposed indication is the treatment of frequent heartburn occurring two or more days a week in adults 18 years of age and older. The sponsor's proposed OTC indication (Uses) is the same as the already approved indication of the currently marketed PPI for OTC use, omeprazole. The proposed directions for use are also basically similar to the OTC label of omeprazole. The following are the product's proposed uses and directions for use:

#### Uses

- treats frequent heartburn (occurs 2 or more days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

#### Directions

- adults 18 years of age and older
- this product is to be used once a day (every 24 hours), every day for 14 days
- it may take 1 to 4 days for full effect, although — people get complete relief of symptoms within 24 hours

b(4)

#### **14-Day Course of Treatment**

- swallow 1 tablet with a glass of water before eating in the morning
- take every day for 14 days
- do not take more than 1 capsule a day
- do not use for more than 14 days unless directed by your doctor

b(4)

#### **Repeated 14-Day Courses (if needed)**

- you may repeat a 14-day course every 4 months
- do not take for more than 14 days or more often than every 4 months unless directed by a doctor

- children under 18 years of age: ask a doctor

#### *Medical Officer Comments:*

- *The proposed OTC label does not include a dose adjustment in patients with severe liver disease. Similar to the prescription label, dose reduction should be considered in patients with severe liver disease. This is because in patients with various degrees of chronic hepatic disease, the mean plasma half-life of lansoprazole was prolonged and the mean AUC was increased (up to 500%) at steady state compared to healthy subjects (see section 5.1, Pharmacokinetics). Therefore, the Directions and Warnings sections of the label should*

*include the following, "Consumers with liver disease, ask a doctor.", or a similar language.*

b(4)

## 8.2 Drug-Drug Interactions

There are no new drug-drug interactions evaluated with this application. There is also no new significant information on drug interactions that warrants any changes in the lansoprazole label.

The prescription label states that lansoprazole (Prevacid) substantially decreases the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole or other PPIs should not be co-administered with atazanavir.

It is theoretically possible that lansoprazole may also interfere with the absorption of other drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Lansoprazole does not have clinically significant interactions with other drugs metabolized through various cytochrome P450 isozymes, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving PPIs, including lansoprazole and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the PPIs was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, PPIs should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with lansoprazole and there was no evidence of a change in the efficacy of lansoprazole.

The proposed OTC label warns the consumer to ask a doctor or pharmacist before use if taking the following drugs: warfarin, prescription antifungal or anti-yeast medicines, \_\_\_\_\_, digoxin, theophylline, tacrolimus, atazanavir \_\_\_\_\_

b(4)

*Medical Officer Comments: The drugs listed in the proposed OTC label are the same drugs listed in the warnings section of another currently marketed OTC PPI, omeprazole, with the addition of 'theophylline' \_\_\_\_\_*

b(4)

*Tacrolimus (an immunosuppressant) was not specifically listed in the Drug Interactions section of the lansoprazole prescription label; however, both drugs are metabolized via the hepatic cytochrome P-450 (CYP)3A4. Lansoprazole may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations. In addition to being a CYP3A4 substrate, lansoprazole is also a CYP2C19 substrate. Patients who are intermediate or poor CYP2C19 metabolizers as compared to those patients who are efficient CYP2C19 metabolizers may have more dramatic increases in their tacrolimus whole blood concentrations which may lead to nephrotoxicity or other side effects.<sup>15</sup> In the tacrolimus prescription label, lansoprazole is included in the list of drugs that may alter tacrolimus concentration. It is important that consumers who are on tacrolimus ask their physicians before taking lansoprazole.*

*The lansoprazole prescription label also states that when administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of the latter was seen which is unlikely to be of clinical concern. The label adds that individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to*

*ensure clinically effective blood levels. The omeprazole prescription label states that in normal subjects, no interaction with theophylline was found; this is probably why theophylline was not included omeprazole OTC label. It would be prudent to include this drug in the OTC label as proposed by the sponsor.*

b(4)

*The prescription label also states that when administered concomitantly with sucralfate, the absorption of PPIs (omeprazole and lansoprazole) was delayed and their bioavailability was reduced by 17% and 16%, respectively. Therefore, PPIs should be taken at least 30 minutes prior to sucralfate. In this reviewer's opinion, the OTC label may remain silent regarding concomitant use with sucralfate because this interaction does not raise a safety issue. If the product does not provide benefit to the consumer, he/she will seek the advice of a physician/healthcare provider.*

There is otherwise no new information regarding drug interaction that precludes the switch of lansoprazole for OTC use; no additional warning is warranted in the proposed lansoprazole OTC label.

### 8.3 Special Populations

No new information regarding special populations was submitted with this NDA to warrant any changes in the lansoprazole label. The following information is reflected in the lansoprazole prescription label.

#### Pregnancy

This application has no new information regarding pregnant women. Lansoprazole is currently listed as Pregnancy Category B. There are no adequate or well-controlled studies in pregnant women. In pregnant rats, teratology studies have been performed at oral doses up to 150 mg/kg/day (40x the recommended human dose based on BSA) and pregnant rabbits at doses up to 30 mg/kg/day (16x the recommended human dose based on BSA) and have revealed no

evidence of impaired fertility or harm to the fetus due to lansoprazole. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The proposed OTC label directs pregnant women to ask a health professional before using the product.

#### Nursing Mothers

It is not known whether lansoprazole is excreted in human milk although the drug and its metabolites are excreted in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from lansoprazole, and the potential for its tumorigenicity shown in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of this drug to the mother.

The proposed OTC label directs pregnant women to ask a health professional before using the product.

#### Geriatrics

The incidence rates of lansoprazole associated adverse events and laboratory test abnormalities are similar to those seen in younger patients. There is no need to alter dosage and administration of lansoprazole in geriatric patients.

#### Renal Impairment

There is no new information in this application on lansoprazole use in patients with renal insufficiency. Similar to the prescription label, no dosage adjustment is necessary in this special population.

#### Hepatic Impairment

No new clinical data has been generated by the sponsor in support of this lansoprazole Rx-to-OTC switch application. There are no changes on the safety profile of lansoprazole with regard to hepatic disease demonstrated in the prescription label and postmarketing surveillance. The lansoprazole prescription label states that a dose reduction should be considered in patients with severe liver disease. In patients with various degrees of chronic hepatic disease, the mean plasma half-life of lansoprazole was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in the mean AUC of up to 500% was observed at steady state in hepatically-impaired patients compared to healthy subjects.

The Directions and Warnings sections of the proposed lansoprazole OTC label should include the following statement, "Consumers with liver disease, ask a doctor", or similar language.

#### Gender

Over 4,000 women were treated with lansoprazole. The incidence rates of adverse reactions in females were similar to those seen in males. In a study comparing 12 male and 6 female human

subjects who received lansoprazole, no gender differences were found in pharmacokinetics and intragastric pH results.

#### Race

The pooled mean PK parameters of lansoprazole from 12 U.S. Phase 1 studies (N=513) were compared to the mean PK parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled U.S. data; however, the inter-individual variability was high. The C<sub>max</sub> values were comparable. No dosage adjustment for Asians is recommended in the prescription label.

### **8.4 Pediatrics**

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population for the proposed indication. The safety and effectiveness of lansoprazole have been established for prescription use in the age group 1 year to 17 years for the short-term treatment of symptomatic GERD and erosive esophagitis; its safety and effectiveness in patients <1 year of age have not been established.

The safety and effectiveness of lansoprazole 15 mg (or any other PPI) for OTC use for the indication of frequent heartburn have not been established for pediatric patients (<18 years old). In most infants with vomiting and older children with regurgitation and heartburn, a history and physical examination is needed to reliably diagnose GERD, recognize complications, and initiate management.<sup>16</sup> Therefore, in the pediatric population, it would be more appropriate to use lansoprazole under the supervision of a physician or a healthcare provider for proper diagnosis and treatment. The sponsor is requesting a waiver to conduct pediatric studies in children < 18 years of age; this request should be granted. Granting this waiver is consistent with the Agency's decision to waive pediatric studies for another drug in the same class and marketed for the same proposed indication, OTC omeprazole.

### **8.5 Advisory Committee Meeting**

There is no Advisory Committee Meeting for this current submission.

### **8.6 Literature Review**

The sponsor performed a review of the worldwide literature to search for information that references lansoprazole utilizing EMBASE (January 1, 1988 to December 31, 2007), MEDLINE, and Novartis internal eNOVA databases (January 1, 1980 to December 31, 2007). There were 157 articles selected by the sponsor for full text review relating to the use of lansoprazole. This reviewer also searched PubMed for published articles that refer to the safety of lansoprazole. The focus of this review will be on articles specifically containing information related to the safety profile of oral lansoprazole in adults. Articles that were written to determine the economic impact of its use or its drug class, or those with no apparent clinical safety significance were

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<sup>16</sup> Pediatric GE Reflux Clinical Practice Guidelines. J Pediatr Gastroenterol Nutr, Vol. 32, Suppl. 2, 2001.

reviewed but will not be discussed. Full reference for these articles can be found in the Appendix section of this review.

The majority of AEs identified from the literature review had been previously identified; the most common were diarrhea and headache. In many placebo-controlled trials, headache was reported with equal frequency in the lansoprazole and placebo groups; 1 case (Castell 1996) was reported severe. Diarrhea was statistically significantly more frequent than the rate observed with placebo; 3 cases (Avner 1995, Chey 2003, Robinson 1995) were reported severe. Other serious labeled events reported in clinical trials were allergy (Avner 1995), increased liver function tests (Robinson, 1995), pharyngitis and nausea/vomiting (Hatlebakk 1993, Chey 2003). Other severe cases reported were dizziness, asthenia, insomnia, and yawning (Chey 2003).

In a 4-year prospective, observational follow-up study, 10,008 patients with a new episode of lansoprazole use (various diagnoses) were followed for a maximum of 2 years to evaluate its safety in the Netherlands. Results showed that adverse events profile and frequency was consistent with results from clinical trials and other observational studies. The most frequently reported adverse events were diarrhea, headache, nausea, skin disorders, dizziness, and generalized abdominal pain/cramps. There were no new rare or unlabelled adverse events of clinical significance recorded. These AEs documented by the prescriber were irrespective of possible association with lansoprazole therapy (Claessens 2000).

One article (Florent, 1994), reported renal colic, a serious unlabeled event, in a patient who was on lansoprazole 30 mg for 4 weeks. The following unlabeled events, not considered serious, have been reported in clinical trials:

- Bigard 2005: cholestasis in one patient taking lansoprazole 15 mg for longer than 4 weeks.
- Chey 2003: laryngismus in a patient on lansoprazole 30 mg for 2 weeks, no outcome reported.
- Hatlebakk 1997: transient diplopia in a patient on lansoprazole 15 mg for 12 months considered to be possibly drug-related.
- Rao 1998: transient decreased stroke volume and cardiac output up to 6 hours in 13 patients taking lansoprazole 30 mg, this was noted with the first dose and was not persistent after one week of treatment.
- Mainz 2002: bitter metallic taste when lansoprazole 30 mg was taken for 4 days in combination with amoxicillin and clarithromycin.
- Portoles 2006: postural hypotension and visual symptoms when ivabradine<sup>17</sup> 10 mg and lansoprazole 60 mg were given together for 5 days; no AEs with lansoprazole alone. The sponsor states that eye symptoms have been reported with ivabradine thought to be attributable to sinus node inhibition and hypotension.
- Sekiguchi 1992: describes increased LDH in a patient after 31 days on lansoprazole 30 mg.

The following unlabeled drug interactions were also found during the search of the literature:

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<sup>17</sup> This drug is used for the treatment of chronic stable angina pectoris. This reviewer did not find ivabradine in the list of U.S. FDA approved drugs.

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- Ahmed 1997: lansoprazole extended the time of vecuronium induced paralysis in an open-label, randomized, placebo-controlled trial.
- Miura 2005: (R and S) enantiomers of lansoprazole were increased by fluvoxamine.

The following case reports/series noted unlabeled adverse events:

- Angles 2002: a 73 y/o with Parkinson's disease on levodopa/benserazide and bromocriptine exhibited akinesia with frequent falls after taking lansoprazole 15 mg for two days.
- Attila 2005: a 52 y/o female on lansoprazole 30 mg daily was diagnosed with carcinoid tumor, duration of treatment was not explicit (at least 2 months). She has diabetes mellitus type I and hypertension. Other diagnoses were bipolar illness 9 years ago and hypothyroidism 23 years ago.
- Bong 2000: an 81 y/o male developed lichenoid drug eruption with PPIs (omeprazole, lansoprazole, and pantoprazole). He was on lansoprazole 30 mg for 3 weeks; rashes resolved after lansoprazole was stopped.
- Bracke, 2005: two cases of subacute cutaneous lupus erythematoses (doses not specified). One was a 69 y/o female taking lansoprazole for 3 months who was also on asthma medications, and the other was a 63 y/o female on estrogens and lansoprazole for 5 months.
- Greco, 1997: glossitis in 6 patients within 7 days of lansoprazole 30 to 60 mg treatment and antibiotics (clarithromycin, metronidazole or amoxicillin).
- Hill, 2007: blue pseudochromhidrosis (growth of malassezia furfur and Bacillus species) on the face and neck in a 57 y/o man following combination treatment with lansoprazole 30 mg for 3 weeks and ranitidine 300 mg twice/day. Condition resolved on stopping both medications and did not recur on restarting lansoprazole only.
- Kazantsev, 2002: a 71 y/o female with intractable GE reflux developed multiple polypoid lesions while being treated with lansoprazole 30 mg for 2 years. Lesions disappeared within 1 year after a Nissen fundoplication; the report stated that it is not possible to say that the lesions were the direct result of chronic PPI therapy.
- Neff, 2002: a 55 y/o female developed acute manic psychosis 3 days after initiation of triple therapy with clarithromycin, amoxicillin, and lansoprazole 30 mg for presumed H. pylori peptic ulcer disease. She also has hypertension, poorly controlled diabetes, arthritis, and dyspepsia; other medications include celecoxib, insulin, glyburide, and lisinopril.
- Prignet, 1996: a 49 y/o male with liver cirrhosis (Child's stage B) developed tremors, imbalance, and confusion after taking lansoprazole. Subsequent investigations disclosed a hematoma to the cerebellum, casting doubt on possible causal relationship with lansoprazole.
- Rajabally 2005: a 42 y/o developed neuropathy after 3 months on lansoprazole (dose not specified).
- Sauvanier 2002: a 92 y/o female was hospitalized for vomiting and dehydration; blood work showed hyponatremia. She was on lansoprazole 30 mg for at least one month; medical history included right kidney stone, old cholecystectomy, hiatal hernia (since 1989), and a recent esophageal stenosis and erosive antritis. The authors stated that it is possible that lansoprazole might complicate hyponatremia.
- Subbiah, 2002: a 46 y/o female was on ranitidine 150 mg 2x/day for 3 months followed by lansoprazole 30 mg; 4 weeks later, she developed tetany which responded with calcium and calcitriol.

Thrombocytopenia is a labeled AE and is one of the most frequently reported AE associated with serious cases reported during postmarketing. There was one case reported (Zlabek 2002) in which an 85 y/o man who presented with an upper GI hemorrhage due to gastric ulcer had thrombocytopenia after 3 days on lansoprazole 60 mg twice daily. Platelet count returned to normal after lansoprazole was discontinued. The authors believed that this was most likely an idiosyncratic thrombocytopenic response to lansoprazole, and whether this was a cause-effect relationship or the result of some other process is not clear.

A retrospective review of exposures reported to the Texas Poison Control from 1998 to 2004 states that PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole) exposure patterns reported to the poison control were generally similar among PPIs and the majority may be successfully managed at home with favorable outcome (Forrester 2007).

There have been reports of hip fractures in elderly patients who are on chronic acid suppression with proton-pump inhibitors particularly at high doses (Yang 2006).

*Medical Officer Comments:*

*The observed adverse events reported in the literature have been previously recorded in other safety databases. Similar to the adverse events from the sponsor's clinical trials, the most commonly reported adverse events in the literature generally relate to the GI system. The most frequently reported adverse event in both the clinical trials and the literature was diarrhea. The adverse events that have not been previously reported had limited clinical information or had no conclusive evidence of a causal relationship between the use of lansoprazole and any previously unidentified adverse events. Most of the adverse events from case reports are short and contain limited information. The duration of use in most cases is 4 months or longer using a dose of lansoprazole 30 mg; this duration of use is longer and dose of lansoprazole is higher in these cases than the proposed OTC use. In addition, most events resolved upon discontinuation of lansoprazole.*

*There have been reports of hip fractures in the literature; these are more of a concern in patients who are receiving prescription lansoprazole for chronic acid-suppression. The proposed OTC use is for a lower dose of lansoprazole (15 mg) and a shorter duration of use (14 days), and not more often than every 4 months unless directed by a doctor. Therefore, if lansoprazole is used according to the OTC label, there should be no concern regarding this safety issue.*

*A review of the published literature did not reveal any new serious, unusual, significant or new safety concerns that would preclude the OTC use of lansoprazole 15 mg for the treatment of frequent heartburn for 2 weeks.*

## **8.7 Postmarketing Risk Management Plan**

There is no postmarketing risk management plan recommended for this NDA beyond routine pharmacovigilance.

## **8.8 Other Relevant Materials**

Division of Medication Error Prevention and Analysis (DMEPA) reviewed the sponsor's proposed name Prevacid 24-HR. See review entered in DFS.

## **9 OVERALL ASSESSMENT**

### **9.1 Conclusions**

The clinical efficacy studies conducted by the sponsor for the indication of frequent heartburn (occurring 2 or more days a week) using lansoprazole 15 mg, and the clinical experience with its prescription use did not identify any new safety concerns that precludes the proposed OTC use for a duration of 14 days. Lansoprazole 15 mg was well-tolerated; the adverse events reported from the study were consistent with the already known adverse events for this drug. From a clinical safety standpoint, this application should be approved.

### **9.2 Recommendation on Regulatory Action**

From a clinical safety standpoint, NCH's proposed lansoprazole 15 mg delayed release capsule indicated for the relief of frequent heartburn occurring two or more days a week for 14 days has an acceptable safety profile for OTC marketing and therefore should be approved. Final approvability depends on the efficacy assessment of the clinical studies conducted for the proposed indication and the DSI inspection.

### **9.3 Recommendation on Postmarketing Actions**

#### **9.3.1 Risk Management Activity**

No special risk management activities are recommended for this NDA beyond routine pharmacovigilance.

#### **9.3.2 Required Phase 4 Commitments**

No required phase 4 commitments are recommended.

#### **9.3.3 Other Phase 4 Requests**

No other phase 4 requests are recommended.

#### 9.4 Labeling Review

Below are the sponsor's proposed labels and product insert. A member of the Interdisciplinary Scientist (IDS) group in the Division of Nonprescription Regulation Development (DNRD) will be reviewing the proposed label and package insert in detail. This Medical Officer has the following general recommendations and comments to the proposed OTC labels:

- The modifier *24HR* in the proposed product's name is not recommended for the following reasons:
  - It may lead consumers to believe that they need to take only one tablet to get full relief and that one pill will be efficacious to treat their frequent heartburn. The recommended course of therapy for lansoprazole is continuous use for 14 days. PPIs generally take 1 to 4 days for full effect.
  - It could be misinterpreted by consumers as relating to the product's duration of action (1 day) or course of treatment (1 day).

*Medical Officer Comments: The trade name reviews entered in DFS for omeprazole OTC (Prilosec 1) during its initial submission were reviewed. In these reviews, the Division of Medications Error (DMETS), now DMEPA, discouraged the use a numeric suffix in conjunction with the proprietary name because suffixes have often been misinterpreted as the product strength or the number of tablets to be administered, and recommended the use of the nomenclature currently utilized by other OTC acid reducers (e.g., Pepcid AC and Axid AR). However, in the current proposed name, the numeric suffix is followed by the letters "HR", and most people know that this is the common abbreviation for hour (Hr). Therefore, the concern for using numeric suffix may not be relevant in this case. See DMEPA's review for the proposed OTC lansoprazole.*

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- Under the Warnings section, Ask a doctor or pharmacist before use if you are taking subsection, the following drugs should be removed from the list: **b(4)**
- The Directions and Warnings sections of the proposed lansoprazole OTC label should include the following statement, "Consumers with liver disease, ask a doctor", or similar language.

In addition, the package insert should reflect the information listed in the PDP and Drug Facts sections of the label.

#### **9.5 Comments to Applicant**

None.

Appears This Way  
On Original

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

### 10.2 Line-by-Line Labeling Review

See section 9.4.

#### Sponsor's Proposed OTC Labels:

Figure A-1: Proposed Prevacid OTC Drug Facts

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       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

**Table A-2: Preferred AE Terms Associated with Fatal Cases (reported at a rate  $\geq 0.3\%$ )  
 (Postmarketing)**

<b>MedDRA SOC / HLT</b>	<b>Death, N (%)<sup>c</sup></b>
<b>Blood and lymphatic system disorders</b>	<b>70 (14.9)<sup>a</sup></b>
Thrombocytopenia	11 (2.3)
Agranulocytosis	10 (2.1)
Leukopenia	10 (2.1)
Pancytopenia	10 (2.1)
Anaemia	7 (1.5)
Disseminated intravascular coagulation	7 (1.5)
Aplastic anaemia	4 (0.9)
Neutropenia	2 (0.4)
Thrombotic thrombocytopenic purpura	2 (0.4)
<b>General disorders and administration site conditions</b>	<b>61 (13.0)<sup>a</sup></b>
Condition aggravated	20 (4.2)
Death	8 (1.7)
Multi-organ failure	8 (1.7)
Pyrexia	7 (1.5)
Malaise	4 (0.9)
Sudden death	4 (0.9)
Chest pain	3 (0.6)
Asthenia	2 (0.4)
Fatigue	2 (0.4)
<b>Hepatobiliary disorders</b>	<b>45 (9.6)<sup>a</sup></b>
Hepatitis	7 (1.5)
Jaundice	7 (1.5)
Hepatic failure	4 (0.9)
Liver disorder	4 (0.9)
Acute hepatic failure	3 (0.6)
Hepatic function abnormal	3 (0.6)
Hepatic necrosis	3 (0.6)
Hepatocellular damage	3 (0.6)
Hepatitis acute	2 (0.4)
Hepatitis fulminant	2 (0.4)
Hyperbilirubinaemia	2 (0.4)

Table A-1 continued...

<b>Gastrointestinal disorders</b>	<b>44 (9.3)<sup>a</sup></b>
Diarrhoea	6 (1.3)
Abdominal pain	4 (0.9)
Haematemesis	4 (0.9)
Dry mouth	3 (0.6)
Gastrointestinal haemorrhage	3 (0.6)
Constipation	2 (0.4)
Dysphagia	2 (0.4)
Melaena	2 (0.4)
Pancreatitis	2 (0.4)
Vomiting	2 (0.4)
<b>Investigations</b>	<b>33 (7.0)<sup>a</sup></b>
Platelet count decreased	4 (0.9)
Blood alkaline phosphatase increased	3 (0.6)
Blood creatinine increased	3 (0.6)
Blood lactate dehydrogenase increased	3 (0.6)
Liver function test abnormal	3 (0.6)
Alanine aminotransferase increased	2 (0.4)
Aspartate aminotransferase increased	2 (0.4)
Blood urea increased	2 (0.4)
Gamma-glutamyltransferase increased	2 (0.4)
White blood cell count decreased	2 (0.4)
<b>Infections and infestations</b>	<b>32 (6.8)<sup>a</sup></b>
Pneumonia	10 (2.1)
Sepsis	9 (1.9)
Infection	2 (0.4)
<b>Skin and subcutaneous tissue disorders</b>	<b>31 (6.6)<sup>a</sup></b>
Toxic epidermal necrolysis	9 (1.9)
Stevens-Johnson syndrome	8 (1.7)
Rash	6 (1.3)
Erythema multiforme	2 (0.4)
Oculomucocutaneous syndrome	2 (0.4)
<b>Cardiac disorders</b>	<b>27 (5.7)<sup>a</sup></b>
Cardiac arrest	6 (1.3)
Myocardial infarction	6 (1.3)
Cardiac failure	5 (1.1)
Atrial fibrillation	2 (0.4)
Bradycardia	2 (0.4)
Cardiac failure congestive	2 (0.4)
Cardiogenic shock	2 (0.4)

Table A-1 continued...

<b>Respiratory, thoracic and mediastinal disorders</b>	<b>22 (4.7)<sup>a</sup></b>
Interstitial lung disease	9 (1.9)
Apnoea	2 (0.4)
Lung disorder	2 (0.4)
Pulmonary embolism	2 (0.4)
<b>Nervous system disorders</b>	<b>20 (4.2)<sup>a</sup></b>
Headache	3 (0.6)
Cerebrovascular accident	2 (0.4)
Depressed level of consciousness	2 (0.4)
Thrombotic stroke	2 (0.4)
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	<b>15 (3.2)<sup>a</sup></b>
Lung neoplasm malignant	2 (0.4)
Oesophageal carcinoma	2 (0.4)
<b>Renal and urinary disorders</b>	<b>12 (2.5)<sup>a</sup></b>
Renal failure	5 (1.1)
Renal failure acute	5 (1.1)
<b>Vascular disorders</b>	<b>11 (2.3)<sup>a</sup></b>
Shock	4 (0.9)
<b>Metabolism and nutrition disorders</b>	<b>11 (2.3)<sup>a</sup></b>
Anorexia	4 (0.9)
Dehydration	2 (0.4)
Hyponatraemia	2 (0.4)
<b>Musculoskeletal and connective tissue disorders</b>	<b>10 (2.1)<sup>a</sup></b>
Arthralgia	2 (0.4)
Muscular weakness	2 (0.4)
Rhabdomyolysis	2 (0.4)
<b>Psychiatric disorders</b>	<b>10 (2.1)<sup>a</sup></b>
Confusional state	2 (0.4)
<b>Injury, poisoning and procedural complications</b>	<b>7 (1.5)<sup>a</sup></b>
Road traffic accident	2 (0.4)
<b>Immune system disorders</b>	<b>5 (1.1)<sup>a</sup></b>
Anaphylactic reaction	2 (0.4)
<b>Total No. of AE Terms</b>	<b>471 (100)<sup>a</sup></b>
<b>Total No. of Cases</b>	<b>215 (100)<sup>a</sup></b>
<b>Total No. of AE Terms / Total No. of Cases</b>	<b>2.2 (100)<sup>a</sup></b>

<sup>a</sup> Totals are those for the entire dataset, not just the data displayed in the table.

<sup>c</sup> Unless otherwise indicated, all percents are calculated based on the total number of AE terms Sponsor's table, Module 5.3.6 –Post-Marketing Report, p.72

**Table A-2: High Level AE Terms Associated with Fatal Cases (≥ 0.5%)  
 (Postmarketing)**

MedDRA SOC / HLT	Deaths N (%)
Blood and lymphatic system disorders	70 (14.9)
Marrow depression and hypoplastic anaemias	15 (3.2)
Thrombocytopenias	13 (2.8)
Neutropenias	12 (2.5)
Leukopenias NEC	10 (2.1)
Anaemias NEC	8 (1.7)
Coagulopathies	8 (1.7)
General disorders and administration site conditions	61 (13.0)
General signs and symptoms NEC	28 (5.9)
Death and sudden death	13 (2.8)
Asthenic conditions	8 (1.7)
Febrile disorders	7 (1.5)
Pain and discomfort NEC	3 (0.6)
Hepatobiliary disorders	45 (9.6)
Hepatocellular damage and hepatitis NEC	18 (3.8)
Cholestasis and jaundice	12 (2.5)
Hepatic failure and associated disorders	7 (1.5)
Hepatic and hepatobiliary disorders NEC	4 (0.9)
Hepatic enzymes and function abnormalities	3 (0.6)
Gastrointestinal disorders	44 (9.3)
Non-site specific gastrointestinal haemorrhages	9 (1.9)
Diarrhoea (excl. infective)	7 (1.5)
Gastrointestinal and abdominal pains (excl. oral and throat)	5 (1.1)
Nausea and vomiting symptoms	3 (0.6)
Oral dryness and saliva altered	3 (0.6)
Investigations	33 (7.0)
Liver function analyses	10 (2.1)
Tissue enzyme analyses NEC	6 (1.3)
Renal function analyses	5 (1.1)
Platelet analyses	4 (0.9)
Infections and infestations	32 (6.8)
Lower respiratory tract and lung infections	12 (2.5)
Sepsis, bacteraemia, viraemia and fungaemia NEC	9 (1.9)
Skin and subcutaneous tissue disorders	31 (6.6)
Bullous conditions	21 (4.5)
Rashes, eruptions and exanthems NEC	6 (1.3)
Cardiac disorders	27 (5.7)
Heart failures NEC	9 (1.9)
Ischaemic coronary artery disorders	6 (1.3)
Ventricular arrhythmias and cardiac arrest	6 (1.3)
Rate and rhythm disorders NEC	3 (0.6)
Respiratory, thoracic and mediastinal disorders	22 (4.7)
Parenchymal lung disorders NEC	10 (2.1)
Breathing abnormalities	3 (0.6)
Respiratory tract disorders NEC	3 (0.6)
Nervous system disorders	20 (4.2)
Central nervous system haemorrhages and cerebrovascular accidents	7 (1.5)
Disturbances in consciousness NEC	3 (0.6)
Headaches NEC	3 (0.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	15 (3.2)

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/s/

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Lolita Lopez  
3/16/2009 08:18:43 AM  
MEDICAL OFFICER

Lesley-Anne Furlong  
3/16/2009 10:24:12 AM  
MEDICAL OFFICER

I concur with Dr. Lopez that the clinical safety  
review supports approval of lansoprazole 15 mg capsules  
for over-the-counter use, pending agreement on labeling.