NDA:	**21-229**
Product:	**Prilosec (omeprazole magnesium tablets 29 mg)**
Sponsor:	**Astra Zeneca/Proctor & Gamble**
Indication:	**Relief and prevention of heartburn**
Marketing:	**OTC**
Submission:	**Safety Update**
Date Submitted:	**Jan, 2000, May, 2000**
Date Received:	**May, 2000**
Date Reviewed:	**August, 2000**
Medical Reviewer:	**Ling Chin, M.D., M.P.H.**

I. INTRODUCTION

Omeprazole was first marketed for clinical use in Europe in 1988, and in the United States (U.S.) in 1989. Since that time, approximately 300 million courses of patient treatments have been prescribed worldwide in 103 countries for various acid-related gastrointestinal disorders, with 90 million courses in the U.S. See Appendix 1.

Omeprazole has been marketed under the trade name LOSEC in Europe and under the trade name PRILOSEC in the United States. Both PRILOSEC and LOSEC are capsules. Omeprazole magnesium (Ome-Mg), the magnesium salt of omeprazole, a tablet, was selected for clinical development for over-the-counter (OTC) use. Results of bridging studies to compare Ome-Mg and omeprazole indicate that their toxicokinetic and toxicological profile are equivalent. Pharmacokinetic studies have demonstrated relative bioavailability between omeprazole capsule and Ome-Mg tablet formulations.

Ome-Mg is approved for prescription use in 26 countries. See Appendix 2. It is available under the trade names of LOSEC, LOSEC tablets, and LOSEC MUPS, since February of 1998. MUPS (multiple unit pellet system) is a disintegrating tablet containing enteric-coated pellets. Ome-Mg is available in Canada as a delayed release (enteric-coated) tablet, which is a different formulation than the MUPS formulation. Ome-Mg is approved for OTC use only in Sweden, available as LOSEC MUPS since 2/1998. Ome-Mg MUPS has never been marketed in the U.S. and is the proposed formulation for OTC marketing.

This is a review of the global post-marketing experience of the Delayed Release and MUPS tablet formulations. The global post-marketing experience of omeprazole capsules will be reviewed by reviewers from the GI division. Safety information from all the OTC trials will be reviewed separately in each individual clinical and actual use study review, and will not be included here.

II. OMEPRAZOLE-MAGNESIUM MUPS TABLET WORLDWIDE POST-MARKETING ADVERSE EVENTS

The safety update included adverse event (AE) reports received by Astra Zeneca (Sweden) since first launch of the MUPS tablet formulation in February 1998 up to December 31, 1999, from all countries where the tablet formulation is marketed. All AE reports associated with omeprazole magnesium MUPS irrespective of indication or causality assessment are included in this summary. This includes reports with very limited information (e.g., inquiries from doctors and pharmacists), provided they contain minimum information required for a report, i.e., an identifiable patient, source, drug and adverse reaction. Consumer reports received during the period are included. The AEs are presented according to the AstraZeneca Adverse Event Dictionary, a modified version of WHOART.

There were a total of 11.6 million patient treatment courses of Ome-Mg distributed to wholesalers during 2/98 to 12/99. There were a total of 219 cases, reporting 398 adverse events. A case represents a single patient who may have more than one adverse event occurring within one or more body systems.

Table 1: Adverse Events reported for MUPS by Body System (2/98-12/99)

Body System	Number Cases	Serious		Non-Serious
		Fatal	Non-Fatal	
Skin and Appendages	35		4	31
Musculo-Skeletal	9			9
CNS and PNS	25		1	24
Vision	8			8
Hearing, Vestibular	1		1	
Special Senses	4			4
Psychiatric	10		3	7
Gastrointestinal	103		5	98
Liver Biliary	6	1	4	1
Metabolic Nutritional	6		1	5
Endocrine	1			1
Cardiovascular, General	2		2	
Myo Endo Pericardial Valvular	1	1		
Heart Rate, Rhythm	2		1	1
Vascular	2		1	
Respiratory	3		1	2
Red Blood Cell Disorders	3		2	1
White Cell and RES Disorders	1		1	
Platelet, Bleeding and Clotting	3		1	2
Urinary	5		2	3
Reproductive	3			3
Body as a Whole	82		7	75
Resistance Mechanism	1		1	
Total Cases*	219	2	25	192
Total AEs*	398	2	44	352

* A single patient is counted as 1 case. However, a single case may have more than one adverse event occurring within one or more body systems. Therefore the numbers of AEs do not coincide with the total number of cases.

Fatal Serious Adverse Events:
There are 2 fatal cases out of a total of 27 serious cases in the reporting period specified. The fatal cases are summarized below:

Case 3991832:
74 y.o. woman with a history of hypertonia and hysterectomy had participated in a clinical study where omeprazole was given as a non-study drug. Three weeks after orthopedic surgery, patient experienced fever, vomiting and pain in the operated knee. She was admitted to the orthopedic unit and transferred to the infectious disease unit for presumptive pneumonia. Omeprazole was given for gastritis. Patient deteriorated, and eventually developed cardiogenic shock and died. Autopsy diagnosis ruled out a myocardial infarct and myocarditis was suspected. The investigator felt that at least 8 drugs were possibly related to the event: omeprazole magnesium, warfarin, cefuroxime, tramadol HCl, erythromycin, cefotaxime, dextropropoxyphene napsilate, and Citodon (codeine and paracetamol).

Case 3992554:
84 y.o. woman treated with omeprazole 80 mg daily for duodenal ulcers. Patient had a history of atrial fibrillation, Type II diabetes and chronic renal insufficiency. Patient was admitted for persistent upper abdominal pain following diagnosis of duodenal ulcer via gastroduodenoscopy. Medications on admission were nitrazepam, Inhibin (hydroquinone, thiamine), domperidone, paracetamol and omeprazole. Several days later, there was a slight deterioration in kidney function with increasing hyponatremia and increasing hyperkalemia. There was a marked increase in LDH level, with considerable increases in the other liver enzymes as well (not noted on admission). Omeprazole was

discontinued and sodium supplements given. A day later, patient died in her sleep. Clinical cause of death was stated as "possibly cardiac due to progressive liver failure, alternatively as a consequence of the medication administered for the recent duodenal ulcer caused by a NSAID."

Medical Officer Comments:
These two fatal cases occurred in elderly women, both of whom were taking several medications concomitantly with omeprazole. In one, omeprazole was given for gastritis, and in the other for duodenal ulcer. In the case of the 74 y.o. woman, her demise occurred in the setting of a serious infection which did not seem responsive to several antibiotics. Death resulted from cardiogenic shock, and there is insufficient information to link omeprazole as the causal agent in this fatality. The 84 y.o. woman who presented with multiple medical problems including chronic renal insufficiency received omeprazole for duodenal ulcers. Omeprazole has been noted to cause elevations in liver enzymes. Rare occurrences of overt liver disease, including some fatal liver necrosis, and hepatic failure is identified in current prescription labeling. Urogenital, including renal, AEs are also listed in prescription labeling. It is known that up to 80% of a dose of omeprazole is excreted renally. Thus, in an elderly woman with multiple medical conditions, including chronic renal insufficiency, the possibility exists that omeprazole may have contributed to the overall demise in this patient. However, there is not enough information to definitively establish omeprazole as the causative agent.

Non-Fatal Serious Adverse Events (SAE):
There were 25 cases of SAEs, which did not result in death, reporting a total of 44 AEs. The sponsor has provided summary tables for the distribution of these cases by body system and WHOART term.

Table 2: SAEs in Most Frequently Occurring Body Systems (Top 4)

Body System	Number Cases	Serious Non-Fatal
Body as a Whole	103	7
Gastrointestinal	82	5
Skin and Appendages	35	4
Liver Biliary	6	4
Hematologic*		4*
Psychiatric	10	3
Urinary	5	2
Red Blood Cell Disorders*	3	2
Cardiovascular, General	2	2

* Sponsor had the hematologic disorders grouped under several body systems such as red blood cell disorders, white cell and reticuloendothelial (RES) system disorders, and platelet, bleeding and clotting disorders. If these AEs were generally grouped under the Hematologic body system, a total of 4 cases would have resulted, and would have placed it in one of the top 5 most frequently occurring body system with reported AEs.

By specific terms, the AEs occurring in the top 5 most frequently occurring body system are as follows:
(1) Body as a Whole: allergic reaction, anaphylactic shock, lack of efficacy, fever, oedema, oedema legs, retrosternal pain, swelling legs
(2) Gastrointestinal: abdominal discomfort, diarrhoea, gastritis, GI haemorrhage, nausea, pancreatitis, stomach pain
(3) Skin and Appendages: angioneurotic edema, exanthema, rash maculo-papular, toxic epidermal necrolysis
(4) Liver Biliary: bilirubinaemia, cholelithiasis, cholestasis intrahepatic, hepatic enzymes increased, hepatic failure (fatal)
(5) Hematologic: pancytopenia, agranulocytosis, purpura thrombocytopenic

Some cases indicative for the specific adverse event within the most frequently occurring body systems are presented below.

Case #19991100368:
65 y.o. female with history of multiple drug sensitivities, was switched to LOSEC MUPS and experienced an allergic reaction characterized by wheezing, and throat swelling, requiring hospital treatment. Previously she was taking LOSEC capsules 10 mg (sometimes 20 mg) QD. Follow-up information stated that she started MUPS on 10/29/99 and her legs began to swell. The next day, she experienced breathing difficulty, and rapid heartbeat with worsening of her leg swelling. She was treated in the ER with parenteral diuretics and discharged on oral diuretics. Omeprazole capsules continued to be taken 11/1 to 11/3, and she experienced leg swelling and breathlessness again. Omeprazole MUPS was discontinued and lansoprazole was initiated with resolution of adverse events. The doctor described the events as oedema to knees and possible left ventricular failure. Allergic reaction was added as an adverse event.

Case #19991100532:
57 y.o. with history of anaphylactic reaction to penicillin, was started on omeprazole 20 mg daily for gastric ulcer disease. One and a half hours after treatment, she experienced anaphylactic shock with urticaria, angioneurotic oedema, and severe bronchospasm. She improved with IV promethazine HCL, IV methylprednisolone+sodium succinate, oxygen, nebulized ipratropium bromide+albutamol sulfate, and was dishcarged 2 hours later on betamethasone and chlorpheniramine..

Case #19991100300:
Male patient with a history of GI bleed switched was switched from LOSEC Capsules (X 4 years) to LOSEC MUPS for about a month. Developed gastritis and gastric discomfort one week after initiating treatment with LOSEC MUPS, and was admitted for GI bleed. Patient commented that LOSEC MUPS was like "taking no treatment at all." Follow up information stated that patient recovered after LOSEC MUPS was stopped and started back on LOSEC capsules.

Case #20000300045:
70 y.o. male patient experienced abdominal pain (retrosternal pain per physician) 4 days after initiating therapy with MUPS 10 mg daily for oesophagitis, Barrett's oesophagus, and peptic ulcer treatment. Event resolved 7 days later when MUPS was stopped, and within 4 hours of initiation with LOSEC capsules. Patient has been treated with LOSEC capsules since '94 without problems.

Case #19991000268:
67 y.o. woman started omeprazole MUPS 10 mg daily and experienced diarrhoea 4 hours later. Diarrhoea continued after intake of MUPS over the next 2 days. Diarrhoea resolved when MUPS was stopped. Switched to omeprazole capsules without problems.

Case #19981200264:
80 y.o. woman with multiple medical problems including longstanding heart and stomach problems, on multiple medications, had been treated with omeprazole capsules 20 mg daily for gastritis. In 11/98, after being switched to omeprazole magnesium tablets, she experienced stomach pain and nausea which required hospitalization for 2-3 days. Omeprazole magnesium was stopped and symtpoms were resolving at time of report.

Case #19991200396:
47 y.o. male with H. pylori-positive reflux oesohagitis, gastritis, and duodenitis was placed on long-term therapy with omeprazole MUPS tablets 20 mg daily. Patient developed gallstones (duration of use not specified) and had increased liver enzymes (ASAT, ALAT, γ-GT, AP) and biliary pancreatitis (highly increased lipase). Patient was hospitalized, omeprazole magnesium was stopped, and had a gallbladder operation. Liver enzymes were not normalized at time of report.

Case #19990800326:
42 y.o. woman was started on omeprazole magnesium 20 mg daily for dyspepsia. After 4 days, she experienced pruritus. Her GP stopped omeprazole and started lansoprazole the next day, along with cetrizine. Hepatic lab values were increased. Her symtpoms deteriorated and 3 days later, she was hospitalized and lansoprazole was stopped. She had icterus, pruritus, dark urine, pale and loose faeces on admission. Ultrasound showed 2 gallstones without bile duct dilatation or cholesystitis. She was given

Vitamin K. One month later she had a liver biopsy which showed intrahepatic cholestasis, which resolved about 3 months later.

Case #19990300019:
42 y.o. woman with goitre and previous cerebral embolism, was started on omeprazole 10 mg daily for reflux oesophagitis. 3 days later, she experienced restlessness, warm skin, increased blood pressure, tachycardia, inreased weight and thirst, dypsnoea, oedema in her legs, and increase in hepatic enzymes. A week later, patient reported reflux oesophagitis symtoms had receeded. 2 days after that, she had drunk up to 9 L and had a weight gain of 4 kg. Omeprazole was stopped about 2 weeks after starting it. Symptoms of thirst, restlessness, and fluid retention were resolving over the next few days, with most symptoms resolving by day of report another 2 weeks later, except for the thirst increase. Concomitant meds: procoumon, levothyroxine sodium.

Case #19990800731: (Sweden)
77 y.o. female previously treated with omeprazole MUPS tablets for 15 days for non-specific gastric disorder, was treated again a month later, with omeprazole 20 mg daily for vomiting. She was also taking paracetamol. The next day, she developed fever, deteriorated general condition and yellow eyes. She was referred to a clinic 3 days later, where the events were assessed as an adverse reaction and both medications were stopped. Patient recovered. Labs noted for low white and neutrophilic counts and high bilirubin.

Case #19990800557:
69 y.o. man with hypertension, complex partial epilepsy, was admitted for seizures 4/25/99 and presumptive cerebral bleed. Treated with phenytoin and diazepam. Upper trunk exanthema appeared 5/6; phenytoin was suspected and stopped. Valproate started same day. Omeprazole MUPS tablets 20 mg daily also started that day for epigastralgia. Other concomitant meds: haloperidol, furosemide, norfloxacin, paracetamol, amlodipine besilate, citalopram hydrobromide. Patient had fever the next day. 5/10, leukopenia and thrombocytopenia were noted. 2 days later, maculopapular rash appeared on upper arms, then lower legs. Omeprazole stopped 5/11. 5/18 agranulocytosis noted. At time of report (8/3), fever, rash, and thrombocytopenia resolved, but agranulocytosis and leukopenia were still present. Omeprazole assessed as possible causal factor.

Case #19991100494:
22 y.o. woman was treated with omeprazole MUPS tablets 40 mg QD for 10 days for gastritis, in early 10/99. On 11/7, she was admitted for a massive GI bleed with thrombocyte value 3/ul. Patient had been experiencing nosebleeding, hematomas on arms and calves and a prolonged menstruation. Concomitant med: diclofenac for dysmenorrhoea. Physical and lab findings significant for petechiae and hematomas on upper, lower extremities, and both mammae, leukocytes 14.2, Hb 10.8, thrombocytes 11G/L, and mild splenomegaly on ultrasound. Bone marrow cytology showed increased megakaryopoiesis consistent with ITP, and no indication of non-Hodgkin's lymphoma. Over 2 weeks, varying doses of systemic prednisolone and immunoglobulins were given, titrated to improving the thrombocyte count which increased to as much as 259 G/L and fell as much as 8 G/L. Pneumococci vaccine and H. flu vaccine were administered and splenectomy was considered. At the time of the report (12/14/99), there was no further information on resolution of events.

Case #19991200423:
Female patient treated with omeprazole, developed pancytopenia and was hospitalized. Concomitant med: metronidazole, fluconazole.

Case #19990900097:
76 y.o. woman with multiple medical conditions (including drug allergies to bactrim, voltaren, and penicillin with shock symptoms) on multiple meds including omeprazole magnesium. Hospitalised 2/99 for syncope associated with drug abuse, and 3/14/99 for reactive depression. On 3/15, patient had fever and a UTI. Over the next 3 days, she developed exanthema, integumental blisters and erosions of oral mucosa and lips, and severe conjunctivitis, noted to be Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TENS) transitional form. The events were considered life-threatening. Patient recovered 4/15/99. Most

suspected drug was Bactrim, but also considered were: lorazepam, lisinopril-HCTZ, tramadol HCl, as well as omeprazole. The UTI and renal insufficiency were also considered as possible causes.

Case #19990300433:
83 y.o. man, previously on omeprazole capsules, was started on omeprazole MUPS tablets for GI angiodysplasias. After 1 hour, he developed angioneurotic edema of the tongue, with subtotal airway obstruction. Treated with histamine antagonists and corticoids and was intubated. Complete regression of oedema in 36 hours. Multiple medical history including cardiac and cardiovascular problems, and renal insufficiency with retention, on multiple medications. Suspected drugs: omeprazole magnesium, allopurinol, HCTZ-enalapril.

Medical Officer's Comments:
These serious AEs were already noted in the prescription labeling, and during the OTC development, specific adverse events of particular concern were to be addressed by the sponsor. These Special Considerations will be reviewed by medical reviewers from the Gastrointestinal and Coagulation Drug Products Review Division.

Non-Serious Adverse Events:
There were a total of 192 cases, reporting a total of 352 AEs, which were non-serious. Table 3 provides a listing of the top 4 Body Systems which has the most AEs.

Table 3: Non-Serious AEs in Most Frequently Occurring Body Systems (Top 4)

Body System	Number Cases	Non-Serious
Gastrointestinal	103	98
Body as a Whole	82	75
Skin and Appendages	35	31
CNS and PNS	25	24

There was no description of the non-serious AEs except for a listing by specific terms. By specific terms, the AEs occurring in the top 4 most frequently occurring body system are as follows:
(1) Gastrointestinal: abdominal discomfort, abdominal pain, abdominal pain upper, acid regurgitation, a belching, bloating, borborygmus, constipation, cramp abdominal, diarrhoea, dyspepsia, dysphagia, epigastric burning, epigastric pain, eructation, faeces discoloured, feeling sick, flatulence, fullness abdominal, gastric pain, gastritis, gastroesophageal reflux, GI symptoms not otherwise specified (NOS), GI tract bleed NOS, heartburn, hyperacidity, indigestion, liver tender, meteorism, mouth disorder, mouth dry, nausea, oral mucosa burning, reflux oesophagitis, stomach burning, stomach cramps, stomach dilatation, stomach pain, stools lose, tongue burning, vomiting, xerostomia
(2) Body as a Whole: abdominal distention, allergic reaction, back pain, lack of efficacy, fatigue, fever, foot oedema, malaise, oedema arm, oedema legs, pain kidney region, pyrexia, swelling inflammatory localized, swollen abdomen, swollen feeling, therapeutic response decreased, tiredness
(3) Skin and Appendages: angioedema, eczema, erythema, exanthema, hair loss, itching, itching localized, itching rash, pruritus, rash, rash arms, rash generalized, rash localized, skin disorder, skin irritation, skin reaction NOS, sweating, sweating increased, swollen lips, urticaria, vesiculobullous rash, arthralgia, arthritis, joint pain, muscle ache, muscle pain, muscle weakness, myalgia
(4) CNS and PNS: balance difficulty, dizziness, headache, paresthesia, paresthesia legs, tenderness behind eyes, tubular vision, twitching eye

Medical Officer's Comments:
Much of the non-serious AEs by specific terms within each body system reported in the MUPS update was also described in the prescription labeling, either from clinical trial data or postmarketing experience, as listed below.
(1) In U.S. clinical trials (≥1% occurrence): headache, diarrhea, abdominal pain, nausea, URI, dizziness, vomiting, rash, constipation, cough, asthenia, back pain.

(2) In international trials (≥1% occurrence): abdominal pain, asthenia, constipation, diarrhea, flatulence, nausea, vomiting, acid regurgitation, headache.
(3) In trials and postmarketing experience (<1% occurrence): AEs from the following body systems were reported: Body as a Whole, Cardiovascular, Gastrointestinal, Hepatic, Metabolic/Nutritional, Musculoskeletal, Nervous System/Psychiatric, Respiratory, Skin, Special Senses, Urogenital, and Hematologic. Fatal cases were noted with pancreatitis, liver necrosis, hepatic failure, toxic epidermal necrolysis, and agranulocytosis.

However, the prescription labeling did not include mention of visual disturbances or eye-related events, which totaled 8 non-serious cases (11.6 million treatments over 2 years) in the MUPS safety update. Overall, the AEs noted to occur with greater frequency were known events.

III. OMEPRAZOLE-MAGNESIUM ENTERIC-COATED TABLET CANADIAN POST-MARKETING ADVERSE EVENTS

A formulation of omeprazole-magnesium tablets different from MUPS was approved in Canada in January 1996 and launched in February 1996. This formulation was called the LOSEC Delayed Release Tablet. See Table 4. A total of 6.4 million treatments were delivered to wholesalers in Canada in that time period. A patient treatment course is counted as one treatment, with the duration of treatment course being 14 or 28 days.

Table 4: LOSEC Delayed Release Tablets in Canada

	First Reporting Period Up to 1/97	Second Reporting Period 2/97-1/98
Treatments	2.7 million	3.7 million
Total Reports	1397	257
Reporting Frequency	0.05% (1 per 2000)	0.007% (1 per 14000)
Total AEs	2335	394
Total SAEs	4	

In the first reporting period, a reporting frequency of 0.05% was observed (one report per 2000 patient treatments). In the second reporting period, the reporting frequency was 0.007% (one report per 14000 treatments). The 4 serious cases in the first reporting period were: 2 cases of angioedema, one case of stomach pain, and one case for lack of efficacy. Table 5 lists the AE reports in the most frequently occurring system organ class for omeprazole capsules and delayed release tablets.

Table 5: Number and (%) AE Reports occurring in most common System Organ Class

System Organ Class	LOSEC Delayed Release Tablets	LOSEC Delayed Release Tablets	Omeprazole Capsules
	Up to 1/97	2/97-1/98	Up to 1/98
GI	914 (65%)	89 (35%)	1601 (20%)
Body as a Whole	744 (53%)	100 (39%)	1342 (16%)
Skin & Appendages	65 (5%)	39 (15%)	1817 (22%)
CNS, PNS	68 (5%)	33 (13%)	1275 (16%)
Psychiatric	20 (1%)	15 (6%)	955 (12%)
Respiratory	16 (1%)	10 (4%)	266 (3%)
Musculoskeletal	13 (1%)	5 (2%)	551 (7%)
Metabolic & Nutritional	4 (0.3%)	9 (4%)	459 (6%)
Liver & Biliary	3 (0.2%)	3 (1%)	400 (5%)
Vision	3 (0.2%)	4 (2%)	294 (4%)
Hematologic*	0 (0%)	1 (0.4%)	568 (7%)
Cardiac & Cardiovascular (all)**	7 (0.5%)	12 (5%)	416 (7%)

* AEs in Red Blood Cell disorders, White Cell and RES disorders, Platelet, Bleeding & Clotting disorders were considered together in Hematologic body system rather than separately.
** AEs in Cardiovascular disorders general, Myo Endo, Pericardial & Valve disorders, Heart Rate & Rhythm disorders, Vascular disorders extracardiac were considered together as Cardiac, Cardiovascular (all) body system rather than separately.

Sponsor noted that the striking difference between LOSEC Delayed Release tablets and Omeprazole Capsules in the first reporting period was due to a greater clustering of events to the GI and Body as a Whole system organ classes with LOSEC tablets. By the second reporting period, the total numbers of AEs had decreased (from 1397 to 237), with the decrease occurring mainly in the GI and Body as a Whole systems. The sponsor attributed this to a decrease of reports of symptoms such as heartburn, nausea, vomiting, and lack of efficacy. The sponsor concluded that, apart from the remaining overrepresentation of reflux symptoms and AEs coded as lack of efficacy, there is no major difference in the adverse event pattern as compared to that of omeprazole capsules.

Medical Officer Comments:
The data reflects the overwhelming clustering of AEs to the GI and Body as a Whole systems in the first reporting period, without an apparent reason. In the first reporting period, within the GI body system, almost all of the reaction descriptions were of symptoms which could reflect the condition for which omeprazole is being used for, such as, heartburn (455 mentions), abdominal pain/discomfort/stomach pain/stomach upset, dyspepsia/epigastric burning, acid indigestion/indigestion, oesophageal burn/discomfort/reflux oesophagitis (149 mentions). Within Body as a Whole, 90% of the mentions were for lack of efficacy (677 mentions). Overall, however, the omeprazole capsule and MUPS tablets experience have continued to show that the top 2 most frequent body systems where the most number of AEs have occurred have been in GI and Body as a whole categories. Therefore, this trend is consistent.

The 4 serious cases in the first reporting period included 2 cases of angioedema, one case of stomach pain, and one case of lack of efficacy. No other information or actual case reports were provided. It is unclear why "lack of efficacy" is a serious case. A review of the line listings of AEs revealed the following:

- mentions of hair loss/alopecia, frequent mentions of rash, but no specific case of TENS
- mentions of decreased/blurry vision; some with resolution, others of unknown outcomes
- numerous GI complaints, a few mentions of hematemesis, melaena, blood in stool, tongue black/brown/swollen, and one mention of an increase in amylase
- mentionsof increased bilirubin/jaundice, hepatitis with no outcome described, and one mention of biliary pain which resolved
- one mention of neonatal thrombocytopenia which resolved. Mother took omeprazole throughout pregnancy
- one mention of gastric polyp with no other information

CONCLUSIONS/DISCUSSION

Omeprazole is generally considered a safe and very effective drug and had been approved recently for long term maintenance therapy. There has been extensive experience with the use of omeprazole capsules worldwide in the last 12 years (300 million treatments). Omeprazole-magnesium MUPS tablets have not been approved for the U.S. market, but is available outside of the U.S. (12 million treatments in the last 2 years). There is also post-marketing experience with omeprazole-magnesium in a delayed release formulation, which is different from the MUPS formulation, in Canada; 6.4 million treatments up to 1/98. As noted in sponsor's submission, the most frequently reported AEs from post-marketing experience has been diarrhea, headache, nausea, abdominal pain, and rash, all of which are listed in current Rx labeling.

The post-marketing experience of the MUPS tablet formulation overall confirms this adverse event pattern. There were cases of serious adverse events in people who switched from the use of omeprazole capsules to the MUPS tablet formulation. Most of these SAEs resolved upon discontinuation of the specific formulation. The full extent of the occurrence of all AEs with a change in formulation to MUPS cannot be assessed since adequate information to do so was not provided by the sponsor.

Much of the adverse events described were known and listed in prescription labeling. However, the post-marketing experience does reflect that rare but very serious, and even fatal cases do occur, in association with the use of omeprazole-magnesium MUPS tablets, albeit in the setting of multiple medical conditions and multiple concomitant medications. While these very serious events involving the liver, pancreas, bone marrow, and skin were considered rare events, the potential for much larger numbers of exposures and thus many more of these events could result from much expanded use by a general population once this drug is available OTC.

Availability in the OTC market invariably results in much greater product sales and therefore much greater exposures by the lay public, without benefit of a learned intermediary to assess their particular risk/benefit situation. One should be assured that, despite easier availability and greater exposures, the overall benefit far outweigh the risks. The sponsor should provide some consideration or estimation of serious events that may be expected with widespread OTC availability to the general public.

RECOMMENDATIONS

The sponsor should provide a reporting rate of the total AEs, SAEs, and deaths relative to the number of treatments prescribed for the MUPS formulation. Based on the experience of similar drug products that have undergone Rx-to-OTC marketing, and the expectation of increased sales with OTC availability, some measure of expected risk/serious events should be estimated. Phase IV surveillance actively monitoring for these serious and potentially fatal cases may need to be in place, so that corrective measures can be instituted in a timely fashion.

Appendix 1

(Registration Life Cycle) Name Contains 'omeprazole'
(Registration Life Cycle) Retracted Date Is No Date '*'
Where the Registration Life Cycles have Registration Submission Records with:
(Registration Submission Record) Purpose Is 'Application'
and the Registration Submission Records have the following product(s):
omeprazole gastro-resistant capsule hard 10 mg, omeprazole gastro-resistant capsule hard 20 mg, omeprazole gastro-resistant capsule hard 40 mg

Country	Product	Submission Date	Original Approval Date	Launch Date
Algeria	omeprazole gastro-resistant capsule hard 20 mg		1993-01-01	1994-02-01
Argentina	omeprazole gastro-resistant capsule hard 10 mg	1995-07-21	1996-01-22	1996-04-01
Argentina	omeprazole gastro-resistant capsule hard 20 mg		1989-12-28	1990-03-30
	omeprazole gastro-resistant capsule hard			
Australia	omeprazole gastro-resistant capsule hard 10 mg	1993-04-19	1994-07-04	1996-02-01
Australia	omeprazole gastro-resistant capsule hard 20 mg	1987-08-31	1988-12-01	1990-05-30
Australia	omeprazole gastro-resistant capsule hard 40 mg	1996-11-29	1997-08-27	1999-03-01
Austria	omeprazole gastro-resistant capsule hard 10 mg	1993-06-29	1995-05-23	1995-10-01
Austria	omeprazole gastro-resistant capsule hard 20 mg	1986-12-12	1990-12-17	1991-06-01
Austria	omeprazole gastro-resistant capsule hard 40 mg	1991-05-22	1993-12-06	1995-10-01
Bahamas	omeprazole gastro-resistant capsule hard 20 mg		1992-03-01	1992-10-01
	omeprazole gastro-resistant capsule hard			
Bahrain	omeprazole gastro-resistant capsule hard 20 mg	1990-01-01	1992-01-07	1993-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Barbados	omeprazole gastro-resistant capsule hard 20 mg		1992-03-01	1992-10-01
Belgium	omeprazole gastro-resistant capsule hard 10 mg	1994-11-24	1996-12-11	1997-06-01
Belgium	omeprazole gastro-resistant capsule hard 20 mg	1986-11-01	1988-12-01	1989-10-30
Belgium	omeprazole gastro-resistant capsule hard 40 mg	1993-05-06	1995-02-21	1997-02-15
	omeprazole gastro-resistant capsule hard			
Brazil	omeprazole gastro-resistant capsule hard 10 mg	1993-05-26	1993-08-26	1994-08-01
Brazil	omeprazole gastro-resistant capsule hard 20 mg	1988-03-14	1990-02-21	1990-10-11
Brazil	omeprazole gastro-resistant capsule hard 40 mg	1994-07-14	1996-10-17	1997-03-06
Cameroon	omeprazole gastro-resistant capsule hard 20 mg		1989-01-01	1989-02-01
	omeprazole gastro-resistant capsule hard			
Canada	omeprazole gastro-resistant capsule hard 20 mg	1987-03-01	1989-06-13	1989-06-30
	omeprazole gastro-resistant capsule hard			

Country	Product	Submission Date	Original Approval Date	Launch Date
	omeprazole gastro-resistant capsule hard			
Chile	omeprazole gastro-resistant capsule hard 20 mg		1990-07-26	1990-11-01
	omeprazole gastro-resistant capsule hard			
China	omeprazole gastro-resistant capsule hard 20 mg		1988-07-27	1990-01-01
Colombia	omeprazole gastro-resistant capsule hard 10 mg	1990-01-01	1996-11-07	1998-01-01
Colombia	omeprazole gastro-resistant capsule hard 20 mg		1991-07-08	1993-08-01
	omeprazole gastro-resistant capsule hard			
Congo	omeprazole gastro-resistant capsule hard 20 mg		1989-01-01	1989-02-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Cyprus	omeprazole gastro-resistant capsule hard 20 mg		1989-05-18	1989-09-01
	omeprazole gastro-resistant capsule hard			
Czech Republic	omeprazole gastro-resistant capsule hard 10 mg	1995-02-15	1996-02-14	1996-09-01
Czech Republic	omeprazole gastro-resistant capsule hard 20 mg	1990-06-17	1992-06-17	1993-03-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Ecuador	omeprazole gastro-resistant capsule hard 20 mg	1994-09-22	1994-12-09	1995-06-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Egypt	omeprazole gastro-resistant capsule hard 20 mg	1988-06-01	1991-02-26	1992-01-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
El Salvador	omeprazole gastro-resistant capsule hard 20 mg		1992-07-28	1992-11-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
France	omeprazole gastro-resistant capsule hard 10 mg	1993-07-22	1996-03-13	1997-10-01
France	omeprazole gastro-resistant capsule hard 20 mg	1986-12-12	1987-04-15	1989-12-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard 20 mg			
Gabon	omeprazole gastro-resistant capsule hard 20 mg		1989-01-01	1989-02-01

Country	Product	Submission Date	Original Approval Date	Launch Date
Germany	omeprazole gastro-resistant capsule hard 10 mg	1993-04-12	1997-03-05	1997-04-15
Germany	omeprazole gastro-resistant capsule hard 20 mg	1986-08-14	1989-10-06	1989-11-01
Germany	omeprazole gastro-resistant capsule hard 40 mg	1990-10-01	1993-02-22	1993-04-01
	omeprazole gastro-resistant capsule hard			
Greece	omeprazole gastro-resistant capsule hard 20 mg	1988-11-22	1989-10-30	1990-04-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Guatemala	omeprazole gastro-resistant capsule hard 20 mg		1991-09-30	1992-02-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Hong Kong	omeprazole gastro-resistant capsule hard 10 mg		1996-01-22	1996-01-22
Hong Kong	omeprazole gastro-resistant capsule hard 20 mg	1987-09-30	1989-01-20	1989-03-01
	omeprazole gastro-resistant capsule hard			
Hungary	omeprazole gastro-resistant capsule hard 20 mg	1989-12-04	1991-07-05	1991-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Indonesia	omeprazole gastro-resistant capsule hard 20 mg	1987-09-30	1988-12-24	1990-10-01
Iran	omeprazole gastro-resistant capsule hard 20 mg			1993-06-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Ireland	omeprazole gastro-resistant capsule hard 10 mg	1993-07-27	1994-07-25	1994-10-04
Ireland	omeprazole gastro-resistant capsule hard 20 mg	1987-06-01	1989-03-16	1989-06-01
Ireland	omeprazole gastro-resistant capsule hard 40 mg	1990-10-11	1992-02-21	1994-04-20
	omeprazole gastro-resistant capsule hard 10 mg			
Israel	omeprazole gastro-resistant capsule hard 20 mg		1990-07-01	1992-04-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Italy	omeprazole gastro-resistant capsule hard 20 mg	1991-03-27	1993-04-17	1993-05-01
	omeprazole gastro-resistant capsule hard			
Ivory Coast	omeprazole gastro-resistant capsule hard 20 mg		1989-01-01	1989-09-01
	omeprazole gastro-resistant capsule hard			
Jamaica	omeprazole gastro-resistant capsule hard 20 mg	1991-05-01	1991-07-05	1992-03-01
	omeprazole gastro-resistant capsule hard			

Country	Product	Submission Date	Original Approval Date	Launch Date
	omeprazole gastro-resistant capsule hard			
Jordan	omeprazole gastro-resistant capsule hard 20 mg	1992-11-01	1993-12-01	1994-05-01
	omeprazole gastro-resistant capsule hard			
Kenya	omeprazole gastro-resistant capsule hard 10 mg	1996-07-01	1997-02-20	1997-06-01
Kenya	omeprazole gastro-resistant capsule hard 20 mg	1988-12-01	1992-07-29	1992-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Kuwait	omeprazole gastro-resistant capsule hard 20 mg	1993-03-01	1993-06-01	1993-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Lebanon	omeprazole gastro-resistant capsule hard 20 mg	1988-11-01	1991-02-01	1991-06-01
Libya	omeprazole gastro-resistant capsule hard 20 mg		1993-05-08	1995-01-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Luxembourg	omeprazole gastro-resistant capsule hard 10 mg	1993-04-27	1995-07-19	1997-11-01
Luxembourg	omeprazole gastro-resistant capsule hard 20 mg	1987-02-01	1987-11-16	1988-02-01
Luxembourg	omeprazole gastro-resistant capsule hard 40 mg		1993-01-07	1993-07-01
	omeprazole gastro-resistant capsule hard			
Malaysia	omeprazole gastro-resistant capsule hard 20 mg	1988-05-11	1989-05-27	1990-05-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Mexico	omeprazole gastro-resistant capsule hard 20 mg	1987-01-01	1990-07-01	1991-01-01
	omeprazole gastro-resistant capsule hard			
Morocco	omeprazole gastro-resistant capsule hard 20 mg		1992-01-01	1993-02-01
Netherlands	omeprazole gastro-resistant capsule hard 10 mg	1993-04-01	1994-02-15	1994-02-28
Netherlands	omeprazole gastro-resistant capsule hard 20 mg	1986-10-01	1988-11-10	1988-12-01
Netherlands	omeprazole gastro-resistant capsule hard 40 mg	1990-06-26	1991-06-18	1992-04-01
Netherlands Antilles	omeprazole gastro-resistant capsule hard 20 mg		1991-06-13	1991-08-15

Country	Product	Submission Date	Original Approval Date	Launch Date
Netherlands Antilles	omeprazole gastro-resistant capsule hard 40 mg		1993-01-27	1993-02-01
	omeprazole gastro-resistant capsule hard			
New Zealand	omeprazole gastro-resistant capsule hard 10 mg	1996-07-05	1997-01-13	1998-01-01
New Zealand	omeprazole gastro-resistant capsule hard 20 mg	1986-11-05	1990-04-19	1990-12-01
New Zealand	omeprazole gastro-resistant capsule hard 40 mg	1997-04-27	1997-10-21	1998-01-01
	omeprazole gastro-resistant capsule hard			
Nigeria	omeprazole gastro-resistant capsule hard 20 mg	1994-03-16	1994-07-29	1994-11-01
	omeprazole gastro-resistant capsule hard 10 mg			
Oman	omeprazole gastro-resistant capsule hard 20 mg	1992-09-27	1993-09-16	1993-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Pakistan	omeprazole gastro-resistant capsule hard 20 mg	1988-11-23	1990-04-17	1991-08-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Panama	omeprazole gastro-resistant capsule hard 20 mg		1992-05-18	1994-06-14
Paraguay	omeprazole gastro-resistant capsule hard 20 mg		1989-12-01	1990-09-01
Peru	omeprazole gastro-resistant capsule hard 10 mg	1996-01-04	1996-01-11	1996-10-01
Peru	omeprazole gastro-resistant capsule hard 20 mg	1994-05-12	1994-06-14	1994-11-01
	omeprazole gastro-resistant capsule hard			
Philippines	omeprazole gastro-resistant capsule hard 10 mg	1993-04-13	1993-10-26	1995-08-01
Philippines	omeprazole gastro-resistant capsule hard 20 mg	1987-11-01	1988-11-02	1989-03-01
Poland	omeprazole gastro-resistant capsule hard 10 mg	1995-10-09	1997-10-28	1998-02-01
Poland	omeprazole gastro-resistant capsule hard 20 mg	1988-11-01	1991-03-12	1991-04-01
	omeprazole gastro-resistant capsule hard			
Portugal	omeprazole gastro-resistant capsule hard 20 mg	1987-10-28	1988-10-04	1989-01-12
Portugal	omeprazole gastro-resistant capsule hard 40 mg	1994-07-27	1998-11-03	1999-11-01
	omeprazole gastro-resistant capsule hard			
Qatar	omeprazole gastro-resistant capsule hard 20 mg	1989-02-11	1991-06-01	1992-05-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			

Country	Product	Submission Date	Original Approval Date	Launch Date
	omeprazole gastro-resistant capsule hard			
Russia	omeprazole gastro-resistant capsule hard 20 mg	1998-09-22	1993-08-11	1993-08-11
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Saudi Arabia	omeprazole gastro-resistant capsule hard 20 mg	1998-01-14	1991-06-17	1991-10-06
	omeprazole gastro-resistant capsule hard			
Senegal	omeprazole gastro-resistant capsule hard 20 mg		1989-01-01	1990-03-01
Singapore	omeprazole gastro-resistant capsule hard 10 mg		1996-09-11	1997-10-01
Singapore	omeprazole gastro-resistant capsule hard 20 mg	1988-04-22	1988-05-25	1989-03-01
	omeprazole gastro-resistant capsule hard			
Slovakia	omeprazole gastro-resistant capsule hard 20 mg		1992-06-17	1993-03-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
South Korea	omeprazole gastro-resistant capsule hard 20 mg	1987-09-30	1989-02-15	1989-05-06
	omeprazole gastro-resistant capsule hard			
Spain	omeprazole gastro-resistant capsule hard 20 mg	1987-03-04	1989-10-17	1989-11-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Sri Lanka	omeprazole gastro-resistant capsule hard 20 mg		1991-10-01	1992-01-01
	omeprazole gastro-resistant capsule hard			
Taiwan	omeprazole gastro-resistant capsule hard 20 mg	1987-11-01	1990-03-14	1990-06-01
Thailand	omeprazole gastro-resistant capsule hard 10 mg	1996-09-13	1997-12-31	1999-03-23
Thailand	omeprazole gastro-resistant capsule hard 20 mg	1987-11-01	1989-03-03	1989-03-31
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Trinidad	omeprazole gastro-resistant capsule hard 20 mg	1991-05-01	1991-08-28	1992-03-01
Tobago	omeprazole gastro-resistant capsule hard 20 mg	1991-05-01	1991-08-28	1992-01-01
Tunisia	omeprazole gastro-resistant capsule hard 20 mg		1992-01-01	1993-01-01
Turkey	omeprazole gastro-resistant capsule hard 20 mg		1991-01-09	1991-03-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			

Country	Product	Submission Date	Original Approval Date	Launch Date
UK	omeprazole gastro-resistant capsule hard 10 mg	1993-03-12	1994-01-06	1994-09-01
UK	omeprazole gastro-resistant capsule hard 20 mg	1986-11-01	1989-05-09	1989-06-01
UK	omeprazole gastro-resistant capsule hard 40 mg	1990-09-03	1992-09-10	1993-09-01
	omeprazole gastro-resistant capsule hard			
United Arab Emirates	omeprazole gastro-resistant capsule hard 20 mg	1988-10-01	1991-06-10	1993-10-01
	omeprazole gastro-resistant capsule hard			
Uruguay	omeprazole gastro-resistant capsule hard 20 mg		1990-05-11	1992-11-01
USA	omeprazole gastro-resistant capsule hard 10 mg	1993-08-27	1995-10-05	1995-10-30
USA	omeprazole gastro-resistant capsule hard 20 mg	1987-12-21	1989-09-14	1989-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Venezuela	omeprazole gastro-resistant capsule hard 20 mg	1991-09-30	1990-10-01	1990-11-01
	omeprazole gastro-resistant capsule hard			
Vietnam	omeprazole gastro-resistant capsule hard 20 mg	1993-05-29	1995-01-04	1995-01-04
Yemen	omeprazole gastro-resistant capsule hard 20 mg	1992-12-14	1993-11-24	1994-04-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Zimbabwe	omeprazole gastro-resistant capsule hard 20 mg		1992-01-20	1993-07-01

Appendix 2

Foreign Marketing Developments – Omeprazole Magnesium Tablets for Prescription Use

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
Argentina	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	31/08/1998	Approved 09/11/1998	30/08/1999
Australia	Losec Tablets	Omeprazole magnesium tablets	10, 20 and 40 mg	08/04/1997	Approved 26/11/1998	01/04/1999
Austria	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	14/02/1997	Approved 24/11/1999	01/01/2000
Belgium		Omeprazole magnesium tablets	10, 20 and 40 mg	06/05/1997	Approved 06/12/1999	
Brazil	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	06/05/1998	Approved 27/11/1998	30/07/1999
	Losec tablets	Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
Denmark	Losec	Omeprazole magnesium tablets	10, 20 and 40 mg	03/02/1997	Approved 22/09/1997	09/03/1998

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
		Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
Finland	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	28/04/1997	Approved 15/12/1997	20/05/1998
France	Mopral	Omeprazole magnesium tablets	10 and 20 mg	13/05/1997	Approved 17/12/1997	
Germany	Antra MUPS	Omeprazole magnesium tablets	10 mg 20 mg 40 mg	11/03/1997 16/01/1997 06/02/1997	Approved 16/11/1998	01/12/1998
	Losec MUPS	Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
Hong Kong	Losec MUPS	Omeprazole magnesium tablets	10 and 20 mg	05/10/1998	Approved 19/02/1999	30/04/1999 (10,20 mg)
	Losec MUPS	Omeprazole magnesium tablets				
Iceland	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	30/10/1997	Approved 07/10/1998	30/10/1998
	Losec MUPS	Omeprazole magnesium tablets				
Ireland	Losec	Omeprazole magnesium tablets	10, 20 and 40 mg	28/11/1997	Approved 17/09/1999	30/09/1999

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
[redacted]		Omeprazole magnesium tablets	[redacted]			
Kuwait	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	30/05/1998	Approved 31/05/1999	
[redacted]		Omeprazole magnesium tablets	[redacted]			
Lithuania	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	05/03/1998	Approved 22/10/1998	
Malaysia	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	09/04/1999	Approved 27/08/1999	01/09/2000
Mexico	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	05/12/1997	Approved 12/06/1998	01/06/1999
[redacted]	osec MUPS	Omeprazole magnesium tablets	[redacted]			
Netherlands	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	01/05/1997	Approved 26/05/1998	30/05/1999
[redacted]		Omeprazole magnesium tablets	[redacted]			
Norway	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	24/01/1997	Approved 04/03/1998	01/09/1998
[redacted]		Omeprazole magnesium tablets	[redacted]			
[redacted]		Omeprazole magnesium tablets	[redacted]			
[redacted]	Losec MUPS	Omeprazole magnesium tablets	[redacted]			
[redacted]	Losec MUPS	Omeprazole magnesium tablets	[redacted]			

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
Russia	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	24/09/1998	Approved 19/03/1999	28/02/2000
Singapore	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	28/05/1998	Approved 27/01/1999	
		Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
South Africa	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	01/04/1997	Approved 11/03/1999	01/04/1999
	Losec MUPS	Omeprazole magnesium tablets				
Sweden	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	30/04/1997	Approved 19/12/1997	02/02/1998 (20 mg) 01/05/1998 (10/40 mg)
Switzerland	Antra MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	07/03/1997	Approved 19/12/1997	01/01/1999
		Omeprazole magnesium tablets				
Thailand	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	02/06/1998	Approved 06/09/1999	
	Losec	Omeprazole magnesium tablets				

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
UK	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	17/10/1997	Approved 07/10/1998	30/08/1999
,Venezuela	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	12/08/1998	Approved 10/05/1999	