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# Safety Profile of Esomeprazole

## Results of a Prescription-Event Monitoring Study of 11 595 Patients in England

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## Abstract

**Objective**: Esomeprazole, the *S*-isomer of omeprazole, was launched in the UK in September 2000. The first proton pump inhibitor, omeprazole, has been marketed in the UK for over 10 years. However, the adverse event database of newly marketed drugs is limited, and it is only after widespread clinical use that the adverse effect profile of a drug is ascertained more comprehensively. This study aims to monitor the safety of esomeprazole prescribed in the primary care setting in England using prescription-event monitoring (PEM).

**Methods**: A postmarketing surveillance study using the observational cohort technique of PEM. Patients were identified from dispensed prescriptions for esomeprazole issued by general practitioners between September 2000 and April 2001. Questionnaires ('green forms') requesting clinical event data on these patients were sent to prescribers approximately 6 months after the date of the first dispensed prescription for each individual patient. Incidence densities (IDs), expressed as the number of first reports of an event/1000 patient-months of exposure (PME), were calculated. Significant differences between IDs for events reported in the first month ($ID_1$) and the following 5 months ($ID_{2–6}$) of exposure were regarded as potential signals. Other methods for signal detection such as medical evaluation of selected events and evaluation of reasons for stopping were also applied.

**Results**: Green forms containing clinically useful information for 11 595 patients (median age 56 years; 53.2% female) were received. Diarrhoea was the event with the highest $ID_1$ in month 1 (8.0 per 1000 patient months of exposure). Adverse events that occurred significantly more often in the first month of treatment with esomeprazole compared with months 2–6 included diarrhoea, nausea/vomiting, abdominal pain, dyspepsia, headache/migraine, intolerance, malaise/lassitude, pruritis, unspecified adverse effects and abnormal sensation.

**Conclusions**: The safety profile of esomeprazole was consistent with the prescribing information and experience reported in the literature.

### Background

The adverse event database of newly marketed drugs is limited,[1] and it is only after widespread clinical use that the adverse effect profile of a drug is ascertained more comprehensively.[2] Esomeprazole, the *S*-isomer of omeprazole, was the first isomer of a proton pump inhibitor (PPI) to become

available for clinical use.[3] It is the fifth PPI to be licensed for use in the UK; the first PPI, omeprazole, has been marketed in the UK for over 10 years. Esomeprazole, like omeprazole, acts by inhibiting the $H^+/K^+$ adenosine triphosphatase enzyme responsible for the secretion of acid by gastric parietal cells.[4] However, esomeprazole was developed to provide a greater degree of acid suppression and a more favourable pharmacokinetic profile, with higher bioavailability and reduced interpatient variability, relative to omeprazole.[4]

Prescription-event monitoring (PEM) is an observational method of postmarketing surveillance used to monitor the safety profile of newly marketed medicines prescribed under primary care conditions in England.[5] The aim of this study was to monitor the safety of esomeprazole prescribed to patients by primary care physicians/general practitioners (GPs) in England.

## Methods

### Identification of Patients and Collection of Data

Patients were identified from dispensed National Health Service prescriptions for esomeprazole issued by GPs in England between September 2000 and April 2001. The data were supplied in confidence by the Prescription Pricing Authority. Simple questionnaires, known as 'green forms' were sent to the prescribing GP at least 6 months after the date of the first prescription for an individual patient. These questionnaires requested information on patient age, indication for prescribing, dose, effectiveness, duration of treatment (start and stop dates), reasons for stopping if applicable, and any events that occurred after the drug was prescribed, including those considered by the GP to have been a suspected adverse drug reaction (ADR). The term 'event' is defined as 'including any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected ADR, any alteration of clinical importance in laboratory values or any other complaint which was considered of sufficient importance to enter in the patient's notes'.

Reported events were coded using the Drug Safety Research Unit (DSRU) event dictionary, a hierarchical dictionary with doctor summary terms grouped under 'lower' terms, which are themselves grouped together under broader 'higher' terms, arranged by system-organ class (SOC). Green forms returned with no information were classified as 'void' and excluded from the study and subsequent analysis because there were no means of determining whether forms which remained uncompleted meant that a patient had not experienced any events.

Each green form returned was reviewed by a DSRU research fellow and the context of each event was assessed. Follow-up information was requested for events of medical importance and those considered medically serious by sending additional questionnaires to the prescribing GP. In addition, follow-up information was requested for events of potential clinical interest based on information available on the safety profile of esomeprazole at the time the study was undertaken. Events from individual case reports were assessed for causal association with esomeprazole using four criteria (temporality, pharmacological plausibility, clinical and pathological characteristics of the event and exclusion of other possible causes) and classified according to one of five categories (probable, possible, unlikely, awaiting further information or not assessable).[6]

Pregnancies occurring during treatment and within 3 months of stopping esomeprazole were also followed up. In cases where the patient had died and no clear cause of death could be established from the green form, further information was sought from the GP to ascertain the certified cause(s) of death.

### Statistical Analysis

Incidence densities (IDs) were calculated for all reported events during treatment with esomeprazole within specified time periods and expressed as the number of first reports of an event per 1000 patient-months of exposure (PME). PMEs were based on those patients for whom either the date of stopping the drug was known or who continued to take the

drug until the end of the study period. IDs for events occurring in the first month of treatment ($ID_1$), during months 2–6 of treatment ($ID_{2–6}$) and for events occurring during the overall treatment period ($ID_A$) were calculated. The difference between the two rates ($ID_1–ID_{2–6}$) and the 99% CIs for this difference were calculated to test the hypothesis that the rate did not change over time. Month 1 is the period when the pharmacologically related events (type A events) are most likely to occur, and events months 2–6 combined are chosen as the reference or 'background' period. In comparing the two periods, assumptions are made that in the background period patients are still exposed, and that event reporting is equivalent in both periods. These two periods are compared (the difference between $ID_1$ and $ID_{2-6}$ is calculated) and the null hypothesis is that there is no change in event rates over time. A possible type A event signal is generated if the difference between $ID_1$ and $ID_{2-6}$ and lower 99% CI is >0.

### Statistical Power for Detection of Adverse Events

The ability to detect an ADR is dependent upon the expected incidence rate of that ADR for those exposed, the background rate of those unexposed and number of patients available. PEM studies aim to identify a cohort size of at least 10 000 patients, which allows one to be 95% certain that any events not observed occur less often than 1 in 3333 cases.[7] A sample size of 10 000 patients should allow for the detection of at least three cases of an ADR, with 85% power, if the reaction occurred at a rate at least 1 in 2000 patients (assuming the background rate is zero).[8] If the background rate of an event was 1 in 1000, a cohort of 10 000 patients would enable detection of an event occurring at a rate of 1 in 500, with 80% power.[9] However, the background rate for many events is not known.

### Ethics

PEM is conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the CIOMS in collaboration with the WHO.[10] The method of study also complies with the Guidelines on the practice of Ethics Committees in Medical Research Involving Human Subjects, as issued by the Royal College of Physicians for records-based research.[11] At the time the study was undertaken, PEM was listed in the Multicentre Research Ethics Committee guidelines for researchers (appendix C) as a method of inquiry and survey conducted in the interest of the public, that does not need reference to an ethics committee.[12]

## Results

### Cohort Size

Green forms were sent for 31 886 patients prescribed esomeprazole between September 2000 and April 2001; 13 263 green forms (41.6%) were returned, of which 11 595 contained useful clinical information. The most frequent reasons for classification of a void were that the patient was no longer registered with the same GP or that a blank form was returned by the GP.

### Patient Demographics

The age and sex distribution is shown in table I. Esomeprazole is not licensed for use in children. Only two patients were <12 years of age. The age was not recorded for 3470 (29.9%) patients.

### Indications for Use

The most frequently reported primary indications were oesophagitis (4570; 39.4%) and gastro-oesophageal reflux disease without oesophagitis (4142; 35.7%). Only 2% of patients received esomeprazole for *Helicobacter pylori* eradication (with antibacterials). The indication was not specified for 5% of the patients.

**Table I.** Patient demographics

| Sex | Number (%) | Median age in years (interquartile range)[a] |
|---|---|---|
| Male | 5 338 (46.1) | 54 (41–66) |
| Female | 6 167 (53.2) | 58 (46–70) |
| Not specified | 90 (0.8) | |
| Total | 11 595 (100) | |

a Age not specified for 3470 patients (29.9% of cohort).

**Table II.** Clinical adverse event terms most frequently given as reasons for stopping esomeprazole

| Higher level term | Number |
|---|---|
| Diarrhoea | 66 |
| Dyspepsia | 61 |
| Intolerance | 60 |
| Nausea/vomiting | 55 |
| Headache/migraine | 43 |
| Pain abdomen | 33 |
| Rash | 25 |
| Unspecified side effects | 25 |
| Malaise/lassitude | 25 |
| Pruritus | 21 |

### Reasons for Stopping Esomeprazole

GPs recorded 5361 reasons for stopping esomeprazole in 5059 patients (43.6% of cohort). The most frequently reported reasons given for stopping esomeprazole were 'condition improved' (1818; 15.7% of cohort) and 'not effective' (1364; 11.8%). With the exception of the non-specific event of 'intolerance', the adverse events were mainly gastrointestinal in nature (see table II).

## Statistical Analysis of Reported Events

'Condition improved' was the event with the highest ID during month 1 ($ID_1$ 93.4 per 1000 PME) and during the entire treatment period ($ID_A$ 31.8 per 1000 PME). Table III shows the adverse clinical events by ranked ID. The adverse events with the highest ranked ID during the first month of treatment ($ID_1$) were gastrointestinal in nature: diarrhoea (7.5 per 1000 PME); nausea/vomiting (7.2 per 1000 PME); and abdominal pain (7.2 per 1000 PME). Events for which there was a positive significant difference between the rate for month 1 ($ID_1$) and months 2–6 ($ID_{2–6}$) included diarrhoea, nausea/vomiting, 'pain abdomen', dyspepsia, headache/migraine, intolerance and malaise/lassitude (see table III). Additional events showing a positive significant difference not included in table III include pruritis, unspecified side effects and 'sensation abnormal' (e.g. hypoesthaesia, paraesthaesia and abnormal sensation).

## Medically Important Events

Table IV presents 101 cases assessed as probably or possibly related to esomeprazole based predominantly on follow-up information obtained from GPs. These events were reported in 71 patients. The SOCs with the greatest number of events considered to be at least possibly related were skin (23; 22.8%) and cardiovascular (19; 18.8%).

Of particular interest were those events under the immunological SOC that may have been suggestive of a hypersensitivity reaction. One event of angioneurotic oedema was assessed as probably related to esomeprazole. A further two events of angioneurotic oedema, one of which occurred in a patient in whom anaphylaxis was also reported, were assessed as possibly related to its use. There were also two events of anaphylaxis that were considered to be possibly related. In addition, events such as rash and urticaria, reported within the skin SOC, may also be indicative of a hypersensitivity reaction. There was one case of urticaria thought to be probably related and four that were possibly related.

Under the cardiovascular SOC, four events of oedema were assessed as possibly related to esomeprazole. These events occurred in patients aged between 59 and 73 years. Oedema was reported in the following areas (one each): leg, fingers, arms and hands. The patient with oedema of the arms and hands was also reported to have oedema of the legs (coded as swollen limb), also considered to be possibly causally related to esomeprazole.

In addition, there were four patients with facial oedema, three of whom were assessed as being possibly related to esomeprazole and the fourth assessed as being probably related. This patient had previously developed angioedema whilst taking lansoprazole.

One event of myocardial infarction was assessed as possibly related to esomeprazole. This event occurred in a 37-year-old male who was a current smoker and was taking warfarin for recurrent deep vein thromboses. The four events of atrial fibrillation, which were assessed as possibly related to esomeprazole, were not pre-existing, and were reported in patients aged between 53 and 79 years of

age, and treatment with esomeprazole was continued in each case. One arrhythmia, which was assessed as possibly related to esomeprazole, concerned a patient who was reported to have an irregular heartbeat.

As can be seen in table IV, nine events were assessed as possibly related to esomeprazole within the eye SOC. The event of visual deterioration, which was reported as decreased vision, 7 months after starting treatment, involved a patient who was reported to be anxious and who frequently reported multiple symptoms. Treatment with esomeprazole was not stopped.

The three events of visual disturbance included two patients who developed blurred vision. The first patient had recurrent amaurosis fugax; the event occurred 5 months after starting treatment and was associated with increased lacrimation. Treatment with esomeprazole was continued when required. The second event, which occurred 8 days after starting treatment, was reported with dizziness; esomeprazole was discontinued and the events resolved. The third event of visual disturbance involved a patient with a history of bilateral cataract surgery, with visual deterioration and dark patches in their visual field >9 months after commencing esomeprazole. Blepharitis was subsequently diagnosed. Treatment with esomeprazole was continued in this case.

In the event of diplopia (time to onset 15 days) and one of the events of teichopsia (time to onset 13 days), esomeprazole was discontinued and the events resolved. The second event of teichopsia occurred in a patient with a history of cataract extraction (time to onset 40 days); treatment with esomeprazole was continued.

Of note, one of the events not included in this table as the follow-up questionnaire was not returned was for a 69-year-old patient who developed visual disturbance of the left eye. A possible diagnosis of optic nerve neuritis was proposed and the patient was referred to a specialist: however, the outcome and final diagnosis are not known.

There were three cases of abnormal liver function tests (LFTs) considered to be possibly related. The first case of abnormal LFTs occurred 5 months after starting esomeprazole, which was not stopped and atorvastatin was considered a possible cause of the abnormality, which was not noted to have resolved. The second event occurred 8 months after starting treatment, and was associated with jaundice. The patient was admitted with collapse, thought to be secondary to a urinary tract infection. Esomeprazole was changed to a PRN (as required) regime and

**Table III.** Incidence densities (ID) for clinical adverse events ranked in order of $ID_1$ per 1000 patient-months

| Higher term description | $N_1$ | $N_2$ | $ID_1$ | $ID_2$ | $ID_1$–$ID_2$ (99% CI) | $N_A$ | $ID_A$ |
|---|---|---|---|---|---|---|---|
| Diarrhoea[a] | 67 | 50 | 7.52 | 1.99 | 5.53 (3.06, 8.01) | 153 | 2.65 |
| Nausea/vomiting[a] | 64 | 51 | 7.19 | 2.03 | 5.16 (2.73, 7.58) | 132 | 2.28 |
| Pain abdomen[a] | 64 | 55 | 7.19 | 2.19 | 5 (2.56, 7.43) | 153 | 2.65 |
| Dyspepsia[a] | 58 | 89 | 6.51 | 3.54 | 2.97 (0.57, 5.38) | 218 | 3.77 |
| Headache/migraine[a] | 47 | 43 | 5.28 | 1.71 | 3.57 (1.47, 5.66) | 119 | 2.06 |
| Respiratory tract infection higher | 40 | 92 | 4.49 | 3.66 | 0.83 (−1.25, 2.91) | 188 | 3.25 |
| Respiratory tract infection lower | 40 | 71 | 4.49 | 2.82 | 1.67 (−0.36, 3.69) | 164 | 2.84 |
| Intolerance[a] | 30 | 24 | 3.37 | 0.95 | 2.41 (0.75, 4.07) | 62 | 1.07 |
| Malaise/lassitude[a] | 29 | 17 | 3.26 | 0.68 | 2.58 (0.97, 4.19) | 71 | 1.23 |
| Pain joint | 24 | 41 | 2.69 | 1.63 | 1.06 (−0.5, 2.62) | 110 | 1.9 |

a Events for which there was a positive significant difference between the rate for month 1 ($ID_1$) and months 2–6 ($ID_{2–6}$).

**$N_1$** = total number of first reports of each event during the first month of treatment; **$N_2$** = total number of first reports of each event during treatment in months 2–6; **$ID_1$** = for each first event during the first month of treatment; **$ID_2$** = for each first event during treatment months 2–6; **$ID_1$–$ID_2$** = arithmetic difference between $ID_1$ and $ID_2$; **$N_A$** = total number of first reports of each event during the total treatment period; **$ID_A$** = for each first event for the total treatment period.

**Table IV.** System organ class (SOC) events (lower term [LT]) assessed as probably or possibly related to esomeprazole

| SOC event – LT | Events during treatment | Events followed-up[a] | Probably related[b] | Possibly related[b] |
|---|---|---|---|---|
| **Immunological** | | | | |
| Anaphylaxis | 2 | 2 | 0 | 2 |
| Angioneurotic oedema | 5 | 4 | 1 | 2 |
| Drug interaction | 2 | 1 | 0 | 1 |
| *Subtotal* | *9* | *7* | *1* | *5* |
| **Cardiovascular** | | | | |
| Arrhythmia | 7 | 7 | 0 | 1 |
| Fibrillation atrial | 12 | 16[c] | 0 | 4 |
| Myocardial infarction | 18 | 1 | 0 | 1 |
| Oedema | 34 | 5 | 0 | 4 |
| Oedema face | 7 | 6 | 1 | 3 |
| Palpitation | 22 | 19 | 0 | 3 |
| Swollen limb | 11 | 1 | 0 | 1 |
| Vasculitis | 1 | 1 | 1 | 0 |
| *Subtotal* | *112* | *56* | *2* | *17* |
| **Eye** | | | | |
| Conjunctivitis | 19 | 1 | 0 | 1 |
| Diplopia | 1 | 1 | 0 | 1 |
| Lacrimation | 2 | 1 | 0 | 1 |
| Teichopsia | 3 | 4[c] | 0 | 2 |
| Vision deteriorated | 1 | 1 | 0 | 1 |
| Visual disturbance | 10 | 12[c] | 0 | 3 |
| *Subtotal* | *36* | *20* | *0* | *9* |
| **Central/peripheral nervous system** | | | | |
| Burning sensation | 6 | 2 | 1 | 2 |
| Dizziness | 73 | 1 | 0 | 1 |
| Headache | 102 | 6 | 2 | 3 |
| Paraesthesia | 17 | 1 | 0 | 1 |
| *Subtotal* | *198* | *10* | *3* | *7* |
| **Alimentary** | | | | |
| Diarrhoea | 153 | 1 | 0 | 1 |
| Dry mouth | 18 | 1 | 0 | 1 |
| Jaundice | 6 | 5 | 0 | 1 |
| Liver function test abnormal | 16 | 16 | 0 | 3 |
| Nausea | 74 | 1 | 1 | 0 |
| Pain abdomen | 153 | 5 | 2 | 0 |
| Swollen tongue | 2 | 2 | 0 | 2 |
| Vomiting | 58 | 1 | 0 | 1 |
| *Subtotal* | *480* | *32* | *3* | *9* |
| **Skin** | | | | |
| Erythema | 1 | 1 | 0 | 1 |
| Erythema nodosum | 2 | 2 | 0 | 1 |

*Continued next page*

**Table IV.** Contd

| SOC event – LT | Events during treatment | Events followed-up[a] | Probably related[b] | Possibly related[b] |
|---|---|---|---|---|
| Hair loss | 9 | 1 | 0 | 1 |
| Photosensitivity | 3 | 4[c] | 0 | 2 |
| Pruritis | 39 | 2 | 1 | 1 |
| Rash | 66 | 17 | 2 | 8 |
| Sore skin | 4 | 1 | 1 | 0 |
| Urticaria | 10 | 9 | 1 | 4 |
| *Subtotal* | *134* | *37* | *5* | *18* |
| **Musculoskeletal** | | | | |
| Muscle weakness | 4 | 1 | 0 | 1 |
| Myalgia | 32 | 7 | 1 | 3 |
| Pain limb | 38 | 3 | 0 | 2 |
| Pain joint | 108 | 4 | 1 | 1 |
| Stiffness | 3 | 1 | 0 | 1 |
| *Subtotal* | *185* | *16* | *2* | *8* |
| **Psychiatric** | | | | |
| Hallucinations | 2 | 2 | 1 | 1 |
| *Subtotal* | *2* | *2* | *1* | *1* |
| **Ear** | | | | |
| Vertigo | 17 | 1 | 0 | 1 |
| *Subtotal* | *17* | *1* | *0* | *1* |
| **Respiratory** | | | | |
| Cough | 57 | 1 | 0 | 1 |
| Dyspnoea | 38 | 1 | 0 | 1 |
| Pharyngitis | 49 | 1 | 1 | 1 |
| *Subtotal* | *144* | *3* | *1* | *3* |
| **Metabolic and endocrine** | | | | |
| Hyponatraemia | 2 | 2 | 0 | 1 |
| *Subtotal* | *2* | *2* | *0* | *1* |
| Haemopoietic | | | | |
| Haematoma spontaneous | 6 | 3 | 0 | 2 |
| Leucopoenia | 3 | 1 | 0 | 1 |
| Red cell abnormal | 3 | 3 | 0 | 1 |
| *Subtotal* | *12* | *7* | *0* | *4* |
| **TOTAL** | **1331** | **193** | **18** | **83** |

a Reports with evidence to suggest that event is not drug-related are not followed-up.

b The difference in numbers between events followed-up and those assessed as possibly or probably related to esomeprazole is accounted for by events assessed as unlikely and events that were not assessable as a result of non-response or incomplete follow-up.

c In addition to events occurring during treatment, follow-up was requested for one or more events that occurred after stopping treatment or where it was not known whether the patient was taking esomeprazole at the time of the event.

8 months subsequently the LFTs were noted to have resolved. The third case occurred 11 months after starting treatment, which was not stopped and the abnormality was reported to have resolved.

## Adverse Drug Reactions

A total of 119 events were reported by GPs as suspected ADRs to esomeprazole for 87 patients (0.75%) [table V]. The most frequently reported

**Table V.** Event terms most frequently reported as adverse drug reactions to esomeprazole

| Lower level term | Number of adverse drug reactions |
|---|---|
| Unspecified side effects | 21 |
| Vomiting | 9 |
| Nausea | 6 |
| Diarrhoea | 9 |
| Dizziness | 8 |
| Headache | 8 |
| Pain abdomen | 6 |
| Malaise | 5 |
| Pruritus | 4 |
| Other[a] | 43 |

a 33 individual events, each reported no more than three times.

ADRs to esomeprazole were unspecified adverse effects, nausea and/or vomiting, diarrhoea, dizziness and headache.

### Pregnancies

There were 13 reports where the patient was known to have been exposed to esomeprazole during pregnancy, all within the first trimester. One of these resulted in delivery by caesarean section for prolonged fetal bradycardia, with subsequent poor fetal condition at birth. Another case resulted in a spontaneous abortion during the second month of pregnancy. There were two reports where esomeprazole was taken within 3 months preceding the patient's last menstrual period. There were no reports of congenital anomalies in these fifteen pregnancies (table VI).

### Deaths

There were 223 deaths (1.9%) reported during the total observation period of this study. There were 57 cases where no information on the patient's cause of death was obtained; these were classified as 'death cause not ascertained'. Of those cases where cause of death was known (n = 166), the patient's death was due to cancer in 60.2% of cases (n = 100) and due to a cardiovascular cause in a further 19.9% of cases (n = 33). The most frequently reported cause of death was myocardial infarction (16/166; 9.6%), followed by 'carcinoma oesophagus' (15/166; 9.0%) and carcinomatosis (14/166; 8.4%). There were no cases where the GP stated on the green form that the patient's death was attributable to esomeprazole.

## Discussion

The patients' reported data in this study were identified from the first patients in general practice in England to be prescribed esomeprazole following its launch in September 2000. One of the principal strengths of PEM is that it examines the use of a drug under normal clinical practice. Unlike in clinical trials, there are no exclusion criteria; the patients cover a wide age range and may be taking medications for a variety of medical conditions. Many of the other studies conducted on esomeprazole are of short duration.[4] Although several thousand patients have been monitored in some of these studies, the duration of the studies has been in the order of 4–8 weeks.[4,13] In this study, for those patients for whom it was known, the average duration of treatment was 26 weeks. Studies that monitored patients for periods of between 6 and 12 months have involved smaller numbers of patients.[4,14] Therefore this PEM study adds a considerable volume of data to the knowledge of the safety of esomeprazole.

A weakness of this study is that only 13 263 of the 31 886 green forms posted to GPs were returned (41.6%) therefore non-response bias may be pre-

**Table VI.** Outcomes of pregnancies for patients treated with esomeprazole

| Exposure to esomeprazole | Total number of pregnancies | Live birth | Spontaneous abortion | Termination of pregnancy | Outcome not ascertained |
|---|---|---|---|---|---|
| Drug stopped before last menstrual period | 2 | 2 | 0 | 0 | 0 |
| Drug taken in 1st trimester | 13 | 10[a] | 1 | 1 | 1 |
| Total | 15 | 12 | 1 | 1 | 1 |

a Caesarean section required for one case of prolonged fetal bradycardia. There was an Apgar score of 4 at 10 minutes.

sent. It may be reasonable to assume that if a patient experienced an event, the GP would be more likely to return the green form, which may introduce reporting bias. However, it is not possible to predict the real direction of any potential bias.

The mean response rate for PEM studies to date is 57%. It is not known why the response rate to this PEM study was lower than the average for PEM studies. However, a possible reason is the GPs' familiarity with PPIs and their confidence regarding their safety. Under-reporting of events including serious or fatal events is also possible in PEM.[15]

One of the advantages of PEM is that through the collection of data on events, signals may be identified for events which GPs have not suspected to be associated with use of the study drug. Signals for possible ADRs to esomeprazole were identified through analysis of the ID for each event and medical review. The most frequently reported adverse events during month 1 were diarrhoea, nausea and/or vomiting, abdominal pain, dyspepsia and headache and/or migraine. Analysis of events where the difference between the rate during the first month of treatment compared with the following 5 months of treatment ($ID_1$–$ID_2$) was statistically significant revealed no new signals. In addition to non-specific events, such as intolerance and unspecified adverse effects, eight other adverse events were identified. Dyspepsia is associated with the indication. Diarrhoea, nausea and/or vomiting, abdominal pain, pruritus and headache are listed in the summary of product characteristics (SPC) as adverse reactions to esomeprazole. Malaise and paraesthesia are only referred to in the prescribing information as adverse reactions to omeprazole which may also be seen with esomeprazole.

PEM studies have previously been conducted on the PPIs omeprazole, lansoprazole and pantoprazole.[16,17] The most common adverse event in the omeprazole, lansoprazole and pantoprazole cohorts was diarrhoea, followed by nausea/vomiting, abdominal pain and headache.

Review of the reasons for stopping esomeprazole and events considered by the GP to be suspected ADRs revealed a similar pattern to the events described above. The most frequently cited events were gastrointestinal events, headache and/or migraine, dizziness and rash. These findings are consistent with those from clinical trials investigating the short-term and long-term use of esomeprazole.[4]

Review of follow-up information from selected events revealed no new signals. The majority of events were included in the SPC either as adverse reactions to esomeprazole or as adverse reactions to omeprazole, which may also be seen with esomeprazole.[18] In the time since esomeprazole was marketed, the SPC has been amended;[19] hypersensitivity reactions, including angioedema and anaphylaxis, have been transferred from adverse reactions to omeprazole to adverse reactions to esomeprazole. Five such events were assessed as possibly or probably related to esomeprazole in this study.

Ocular events are of interest with proton pump inhibitors following the publication of a case series in 1997 of nine patients reported to a monitoring unit for serious ADRs in Germany.[20] Five of the nine patients had received intravenous omeprazole. Six patients developed ischaemic optic neuropathy, one patient developed ischaemic retinopathy, and blurred vision was reported in the remaining two patients. The authors proposed that PPIs, as a result of their pharmacological action, may possibly induce vasoconstriction and ischaemia in end arteries such as the retinal artery. However, this hypothesis prompted responses debating this conclusion.[21,22] The ocular safety of anti-ulcer drugs (including omeprazole but not esomeprazole), has been examined in a cohort of almost 140 000 patients using a UK healthcare database.[23] The authors concluded that the results of this study did not suggest a major increased risk for vascular or inflammatory diseases of the eye associated with the use of omeprazole or other anti-ulcer drugs.

Overall, only a small number of reports of ocular events during treatment with esomeprazole were reported in this PEM study. The limited information provided for ocular events in this study makes it difficult to interpret the findings.

PPIs are used during pregnancy to treat gastro-oesophageal reflux; therefore, it is important that pregnancy outcomes are monitored. No cases of congenital anomaly were reported for any of the fifteen pregnancies monitored during this study. The safety of PPIs in pregnancy has been studied extensively elsewhere using a variety of techniques including a multicentre prospective controlled trial, analysis of a national birth registry, a meta-analysis of published studies and analysis of healthcare databases.[24-27] These studies have concluded that the use of omeprazole and other PPIs (not including esomeprazole) is not associated with a major teratogenic risk.

A total of 223 deaths were reported during the study. In the majority of cases where cause of death was known (n = 166), the patient's death was due to cancer (60.2%) or due to a cardiovascular cause (19.8%). These findings should be considered in context with the age of the population undergoing treatment and the indications for use. A recent mortality study compared almost 18 000 patients prescribed omeprazole from 1993 to 1995 with the general population in the UK.[28] Observed mortality for all causes was higher in the first year after registration; however, by year 4 this had fallen to population expectations. During the first year of the study, approximately 40% of deaths were from disorders of the circulatory system, 30% from neoplasms and a further 15% from disorders of the respiratory system. A higher proportion of deaths secondary to cancer was seen in this PEM study compared with the first year of the mortality study. There are several possible explanations for this, including a possible change in the prescribing of PPIs since 1995 with an increase in their use in patients with cancer for symptom relief. The authors of the mortality study concluded that increases in mortality still present at year 4 for some causes of death at the individual International Classification of Diseases chapter level were due to pre-existing illness, including pre-existing severe oesophageal disease.

## Conclusions

This study examined the use of esomeprazole in 11 595 patients in the community and reflects real-world use. No new signals for ADRs were identified. Analysis of selected events, outcomes from pregnancies and deaths also revealed no unexpected findings. It is very likely that this can be accounted for by the extensive postmarketing experience with omeprazole. Overall, the safety profile of esomeprazole was consistent with the prescribing information and experience reported in the literature.

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