STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Nexium capsules
ACTIVE INGREDIENT: Esomeprazole Magnesium Hydrate

Study No: D961PC00002
NCT01729182

Developmental Phase: post-marketing
Study Completion Date: March 2017
Date of Report: June 2017

OBJECTIVES:

The objectives of the S-CEI was to evaluate the efficacy (in terms of the proportion of patients free of peptic ulcer recurrence), determine the nature and frequency of adverse drug reactions, and identify potential factors affecting the safety and efficacy of Nexium Capsule when actually used in clinical practice for reduction of the risk of gastric or duodenal ulcer recurrence associated with low-dose aspirin treatment.

METHODS:

Observational Study

RESULTS:

1. Persistence of Treatment with Nexium Capsule

During the observation period in 2295 patients in the safety analysis set, treatment with Nexium Capsule continued for ≥12 weeks in 2074 patients (90.4%), ≥24 weeks in 1977 patients (86.1%), ≥36 weeks in 1900 patients (82.8%), ≥52 weeks in 1804 patients (78.6%), ≥64 weeks in 1668 patients (72.7%), ≥76 weeks in 1609 patients (70.1%), ≥88 weeks in 1573 patients (68.5%), and ≥104 weeks in 1283 patients (55.9%).

Treatment with Nexium Capsule was permanently discontinued during the observation period of the S-CEI in 732 patients (31.9%). The most common reason for discontinuation was being lost to follow-up (e.g., change of hospital, change of residence) in 375 patients, followed by other reasons (e.g., patient's decision, switching to another

medication) in 265 patients, adverse events in 63 patients, and insufficient efficacy in 29 patients.

2. Safety

(1) Of 2295 patients in the safety analysis set, 63 patients (2.7%) reported at least one adverse drug reaction (ADR). The most common ADRs were gastrointestinal disorders reported in 25 patients (1.1%). ADRs reported in 3 or more patients included constipation in 8 patients (0.3%), diarrhoea in 5 patients (0.2%), death in 4 patients (0.2%), and anaemia, abdominal distension, dyspepsia, and pruritus in 3 patient (0.1%) each.

In clinical studies (LDA trials) conducted up to the marketing approval, the proportion of patients with at least one ADR (hereinafter, incidence of ADRs) was 14.5% (31/214 patients). Although direct comparison is difficult because of different patient background characteristics and other conditions, the incidence of ADRs was lower in the S-CEI.

A total of 17 serious ADRs were reported in 14 patients: 4 events of death, and 1 event each of sepsis, colon cancer, gastric cancer, anaemia, autoimmune thyroiditis, cerebral haemorrhage, dementia of the Alzheimer's type, loss of consciousness, haemoptysis, pneumonia aspiration, colitis ischaemic, haematemesis, and autoimmune hepatitis. None of the reported serious ADRs were definitely related to Nexium Capsule.

Unanticipated ADRs reported in at least 3 of 63 patients with any ADR were death (4 patients), and anaemia and dyspepsia (3 patients each). Except for 4 cases of death, all of them but anaemia in 1 patient was non-serious.

ADRs of special interest in the S-CEI included community-acquired pneumonia, Clostridium difficile-associated enterocolitis, and colitis microscopic, which were suspected to be related to treatment with PPIs and were to be collected and reviewed post-marketing. No cases of any of these ADRs were reported in the S-CEI.

A total of 18 events of fracture-related AEs were reported in 17 patients: 4 events of femoral neck fracture, 3 events of spinal compression fracture, 2 events each of femur fracture and tibia fracture, and 1 event each of fracture, osteoporosis, radius fracture, rib fracture, ulna fracture, lumbar vertebral fracture, and fibula fracture. Among these fracture-related AEs, 1 case of osteoporosis was the only one suspected to be causally related to Nexium Capsule, while it was a non-serious ADR. Fracture-related AEs reported in the S-CEI were primarily consisted of fracture in elder post-menopausal female patients with complications such as diabetes mellitus and osteoporosis. No safety concern specific for Nexium Capsule was identified.

Incidences of ADRs in different periods of treatment were as follows: 1.3% (30/2295 patients) in <Week 12, 0.4% (8/2074 patients) in Week 12 to <Week 24, 0.3% (6/1977 patients) in Week 24 to <Week 36, 0.3% (6/1900 patients in Week 36 to <Week 52, 0.2% (3/1804 patients) in Week 52 to <Week 64, 0.1% (1/1668 patients) in Week 64 to<Week 76, 0.2% (4/1609 patients) in Week 76 to <Week 88, 0.4% (6/1573 patients) in Week 88 to <Week 104, and 0.2% (2/1283 patients) in Week 104 and subsequently. There was no increasing tendency in the incidence of ADRs associated with increased treatment duration.

Investigation of factors potentially affecting the safety revealed following factors showing a significant difference ($P<0.05$): smoking habit ($p=0.0027$), modification of treatment with Nexium Capsule ($p=0.0029$), adherence to Nexium Capsule treatment

(p=0.0304), and continuation/discontinuation of Nexium Capsule treatment (p<0.0001). However, no new safety concern attributable to Nexium Capsule was identified.

(2) Serious adverse events (SAEs) were reported in 191 of 2295 patients (8.3%) in the safety analysis set.

SAEs reported in at least 3 patients included pneumonia in 19 patients (0.8%), cardiac failure in 11 patients (0.5%), gastric cancer and angina pectoris in 10 patients (0.4%) each, death and fall in 6 patients (0.3%) each, colon cancer, lung neoplasm malignant, and cardiac failure chronic in 5 patients (0.2%) each, cerebral infarction, myocardial infarction, myocardial ischaemia, pneumonia aspiration, renal failure, femoral neck fracture, and subdural haemorrhage in 4 patients (0.2%) each, and sepsis, oesophageal carcinoma, pancreatic carcinoma, anaemia, dementia of the Alzheimer's type, cardiac failure congestive, peripheral arterial occlusive disease and spinal compression fracture in 3 patients (0.1%) each. Causal relationship with Nexium Capsule was ruled out for SAEs except for sepsis, colon cancer, gastric cancer, anaemia, autoimmune hepatitis, dementia of the Alzheimer's type, loss of consciousness, haemoptysis, pneumonia aspiration, colitis ischaemic, haematemesis, and autoimmune hepatitis in 1 patient each and death in 4 patients.

A total of 69 cases of SAEs with an outcome of death were reported in 58 patients, which included 6 cases each of pneumonia, cardiac failure, and death as well as 3 cases each of lung neoplasm malignant, pneumonia aspiration, and renal failure. Causal relationship with Nexium Capsule could not be ruled out for 4 cases of deaths and 1 cases each of loss of consciousness, haemoptysis, and haematemesis but was unclear for all of these events.

There was no increasing tendency in the incidence of adverse events (AEs) associated with increased treatment duration. Specifically, incidences of SAEs in different periods of treatment were as follows: 1.6% (37/2295 patients) in <Week 12, 1.2% (24/2074 patients) in Week 12 to <Week 24, 1.4% (27/1977 patients) in Week 24 to <Week 36, 1.9% (37/1900 patients in Week 36 to <Week 52, 1.3% (24/1804 patients) in Week 52 to <Week 64, 1.6% (26/1668 patients) in Week 64 to<Week 76, 1.1% (17/1609 patients) in Week 76 to <Week 88, 1.7% (27/1573 patients) in Week 88 to <Week 104, and 0.5% (7/1283 patients) in Week 104 and subsequently.

3. Efficacy

The efficacy of Nexium Capsule was evaluated using data on the proportion of patients free of peptic ulcer recurrence and on subjective symptoms.

(1) Non-recurrence rate of peptic ulcers

1) Of 2104 patients in the efficacy analysis set, 553 patients (26.3%) underwent endoscopy after starting treatment with Nexium Capsule. Among these 553 patients, no peptic ulcer (i.e., active [A1 or A2] or healing [H1 or H2] according to the Sakita-Miwa classification system) was found in 535 patients (96.7%) at Week 52 and in 528 patients (95.5%) at Week 104 of the treatment.

2) In 553 patients with at least one endoscopic assessment between the start of Nexium Capsule treatment and the end of the observation period or treatment discontinuation, the non-recurrence rate was 98.5% (95% confidence interval [CI]: 97.4%, 99.5%) at Week 12, 97.8% (95% CI: 96.6%, 99.1%) at Week 24, 97.4% (95% CI: 96.0%, 98.8%) at 36

Week, 96.4% (95% CI: 94.7%, 98.1%) at Week 52, and 92.7% (95% CI: 89.6%, 95.9%) at Week 104.

3) No significant difference ($P<0.05$) was observed for any patient background factors and treatment factors except for smoking habit ($p=0.0452$) and adherence to LDA ($p=0.0065$). No new safety concern attributable to Nexium Capsule was identified.

(2) Subjective Symptoms

1) Among patients who had particular subjective symptoms at the start of treatment, the proportions of patients experiencing improvement in the particular subjective symptoms were as follows: 89.3% (316/354 patients) for epigastric pain, 84.3% (268/318 patients) for inappetence, 85.4% (263/308 patients) for abdominal distension, 91.4% (465/509 patients) for heartburn, 91.6% (152/166 patients) for nausea, 91.9% (57/62 patients) for vomiting, and 87.2% (232/266 patients) for eructation.

2) Proportions of patients experiencing resolution of particular subjective symptoms of gastric or duodenal ulcer were as follows: 83.9% (297/354 patients) for epigastric pain, 76.7% (244/318 patients) for inappetence, 80.2% (247/308 patients) for abdominal distension, 86.1% (438/509 patients) for heartburn, 88.6% (147/166 patients) for nausea, 88.7% (55/62 patients) for vomiting, and 79.7% (212/266 patients) for eructation.

3) The subjective symptoms of gastric or duodenal ulcers improved as soon as treatment with Nexium Capsule started and all of the subjective symptoms except for heartburn resolved in more than 90% of the patients at Week 12 or later.