**STUDY REPORT SUMMARY**

**ASTRAZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:** Nexium capsules
**ACTIVE INGREDIENT:** Esomeprazole Magnesium Hydrate

| **Study No: D961HC00012** |
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| NCT01562600 |

**Developmental Phase:** post-marketing
**Study Completion Date:** August 2015
**Date of Report:** June 2017

**OBJECTIVES:**

The objectives of this study were to confirm efficacy, ADR development, and factors which may affect safety and efficacy of the long term use of NEXIUM for prevention of recurrence of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug (NSAID).

**METHODS:**

Observational Study

**RESULTS:**

**1. Treatment period of NEXIUM in the observation period**

The continuous treatment periods of NEXIUM in the safety analysis set of 1521 patients during the observation period were as follows: "≥ 12 weeks" 75.9% (1155 patients), "≥ 24 weeks" 67.3% (1023 patients), "≥ 36 weeks" 62.4% (949 patients), and "≥ 52 weeks" 48.7% (740 patients).

The number of the patients in whom NEXIUM was discontinued during the observation period was 662 (43.5%). The major reason of discontinuation according to the classification in the CRF was "Others (e.g. discontinuation of NSAID, improvement of symptoms, and according to the request from the patient)" in 327 patients, followed by "Discontinuation of treatment visit during the observation period (e.g. patients changed

hospital, or change of their houses) in 292 patients, “Subtherapeutic response” in 23 patients, and “Adverse event” in 20 patients.

## 2. Safety

### (1) Adverse drug reactions (ADRs)

In the safety analysis set of 1521 patients, 38 events of ADRs were reported in 26 patients (1.7%). ADRs reported in at least 2 patients (0.1%) were: neuropathy peripheral, hypertension, upper respiratory tract inflammation and osteoporosis. While a direct comparison is difficult between data in the post-marketing surveillance and those in clinical studies, the ADR frequency was remarkably lower in the S-CEI compared to the ADR frequency (15.2% 46/303 patients) in Phase III control study and long-term study in Japanese patients with NSAID therapy which had been conducted before approval.
Serious ADRs were: diffuse large B-cell lymphoma, gastric cancer, subarachnoid haemorrhage, arrhythmia, atrioventricular block complete, cardiac failure acute, aortic embolus, colitis ischaemic, wrist fracture and pelvic fracture reported in each one patient.
ADRs unexpected from the NEXIUM prescribing information were neuropathy peripheral, hypertension, upper respiratory tract inflammation and osteoporosis in each 2 patients; and infection, pneumonia, diffuse large B-cell lymphoma, gastric cancer, iron deficiency anaemia, hyperlipidaemia, subarachnoid haemorrhage, cerebral haematoma, erythema of eyelid, arrhythmia, atrial fibrillation, atrioventricular block complete, cardiac failure acute, aortic embolus, cough, colitis ischaemic, gastrointestinal sounds abnormal, costochondritis, chest discomfort, fall, wrist fracture and pelvic fracture in each one patient.
The ADR frequencies classified by onset periods after starting NEXIUM were as follows: “< 12 weeks” 1.1% (17/1521), “≥ 12 weeks and < 24 weeks” 0.4% (5/1155), “≥ 24 weeks and < 36 weeks” 0.5% (5/1023), “≥ 36 weeks and < 52 weeks” 0.4% (4/949), and “≥ 52 weeks” 0% (0/740). ADR frequencies did not increase along with longer treatment period.
In the S-CEI, it was required to collect and review information of the events of fracture, community acquired pneumonia, chlostridium difficile enterocolitis in the post-marketing setting because causal relationship between each event and PPI had been suspected. In the S-CEI, development of these ADRs was investigated: chlostridium difficile enterocolitis was reported in one patient; pneumonia as an event of community acquired pneumonia and fracture were reported in each one patient; and wrist fracture and pelvic fracture as events of fracture were reported in each one patient.
As above, there was no new safety issue in the frequency of ADRs and ADR development profile observed in the S-CEI.

### (2) Adverse events

In the safety analysis set of 1521 patients, 72 events of serious adverse events were reported in 49 patients (3.2%).
Serious adverse events reported in at least two patients were: cerebral infarction in 5 patients (0.3%), pneumonia in 4 patients (0.3%), gastric cancer in 3 patients (0.2%), colon cancer, metastases to liver, cerebral haemorrhage and subarachnoid haemorrhage in each two patients (0.1%). Causal relationship between each event and NEXIUM was ruled out in these patients other than pneumonia, gastric cancer and subarachnoid haemorrhage in each one patient.
Serious adverse events of fatal outcomes were reported in 16 patients. The events were: colon cancer and metastases to liver in each two patients, pneumonia, pneumonia

staphylococcal, sepsis, septic shock, prostate cancer, adrenal gland cancer, subarachnoid haemorrhage, embolic cerebral infarction, cardiac failure acute, cardiac failure congestive, coronary artery stenosis, aspiration, pulmonary fibrosis, pulmonary haemorrhage, intestinal obstruction and road traffic accident in each one patient.
As above, there was no new safety issue in the development profile of serious adverse events observed in the S-CEI.

**3. Efficacy**

The efficacy of NEXIUM was reviewed according to the data of non-recurrence rate of peptic ulcers and subjective symptoms.

**(1) Non-recurrence rate of peptic ulcers**

1) In the efficacy analysis set of 1303 patients, the proportion of the patients without any peptic ulcer (active ulcer (classified as A1, A2, H1 or H2) according to Sakita-Miwa classification was 91.2% (187 patients) of 205 patients who underwent endoscopy after NEXIUM was started (15.7%).
2) The non-recurrence rates of peptic ulcers in 205 patients were as follows: 92.7% at treatment week 12 (95% CI 89.1-96.4%); 90.7% at treatment week 24 (95% CI 86.4-94.9%); 89.9% at treatment week 36 (95% CI 85.4-94.4%); 89.9% at treatment week 52 (95% CI 85.4-94.4%).

**(2) Subjective symptoms**

1) The improvement rates of subjective symptoms in the patients who had subjective symptoms at the baseline were as follows: epigastric pain 93.5% (302/323), inappetence 87.6% (289/330), bloating 87.8% (260/296), heartburn 93.1% (363/390), nausea 92.1% (175/190), vomiting 95.5% (63/66) and gaseous regurgitation 86.8% (171/197).
2) The resolution rates of subjective symptoms in patients who had gastric or duodenal ulcer were as follows: epigastric pain 90.1% (291/323), inappetence 80.6% (266/330), bloating 80.7% (239/296), heartburn 89.7% (350/390), nausea 90.0% (171/190), vomiting 95.5% (63/66) and gaseous regurgitation 82.2% (162/197).
3) All subjective symptoms were improving after NEXIUM was started in view of the change of severity of them during the observation period. All subjective symptoms except inappetence and bloating resolved at least 12 weeks after starting NEXIUM in ≥90% of the patients who had the symptoms at baseline.