AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Nexium capsules
ACTIVE INGREDIENT: Esomeprazole Magnesium Hydrate

Study No: D961HC00013
NCT01562639

Developmental Phase: post-marketing
Study Completion Date: July/2014
Date of Report: June/2015

OBJECTIVES:

The objectives of this study were to investigate efficacy (non-recurrent rate of reflux oesophagitis (RE)), characteristics of ADRs, the factors which may affect efficacy and safety, and efficacy and safety of the NEXIUM dose 20 mg daily in patients given NEXIUM as the maintenance therapy for recurrent/relapsing RE.

METHODS:

Observational Study

RESULTS:

1. Ongoing use of NEXIUM in these patients

In the 601 patients of the safety analysis set, the length of observation period was longer than 26 weeks in 60.6% (364 patients), and 167 patients (27.8%) discontinued NEXIUM during the observation period in the S-CEI. The most common reason of the discontinuation was “no visit of the patients (e.g. due to change of the hospital or of the house) in 72 patients, followed by “improvement of the RE symptoms” in 58 patients, “Others (patient's request, and change to other drug etc)” in 20 patients, “ineffectiveness” in 9 patients and “adverse events” in 8 patients.

2. Safety

(1) Total 15 events of ADRs were observed in 10 of the 601 patients (1.7%) of the safety analysis set. No ADRs developed in three or more patients: upper abdominal pain was reported from 2

patients (0.3%), and other ADRs were individually experience by one patient, and all of them were non-serious. In 10 patients who experienced ADRs, ADRs unexpected from the NEXIUM JPI were each one event of bronchitis, eyelid eczema and chronic gastritis.
Fracture, community acquired pneumonia, and enterocolitis in association with Clostridium difficile infection were the events which had been considered possibly related to PPIs, and for which safety information should be collected after marketing. Confirmation of the data of these events in this S-CEI revealed one patient who had femoral neck fracture as a fracture event. However, the factor of the fracture was fall, and there were no significant findings concerning causality with NEXIUM.
Direct comparison of ADR incidence is difficult between the data of the pivotal clinical study for the RE maintenance therapy for JNDA and of S-CEI because patient demography data and treatment factors are different between them. However, the ADR incidence was lower in the S-CEI data than the clinical study data (9.8% (26/264)).

(2) 9 serious adverse events were reported in 7 of 601 patients (1.2%). All adverse events were unlisted in the NEXIUM JPI: these included, one event of, gastric cancer, metastases to bone, pancreatic carcinoma, hepatocellular carcinoma, cardiac disorder (reported AE term "aggravation of cardiac disease"), pulmonary haemorrhage, back pain, chest discomfort and femoral neck fracture. The events of fatal outcomes were observed in three patients, but causal relationship between each event (including deaths) and NEXIUM was ruled out.

(3) Between the patient demographic factors and the treatment factors, the factor which showed significant difference of ADR development ($P<0.05$) was only the discontinuation vs no discontinuation of NEXIUM ($p=0.0008$), and there were no remarkable findings in these data. In addition, there was no significant difference in the ADR incidences between the 10 mg dose group and the 20 mg dose group at the time of starting the maintenance therapy ($p=0.3347$).

3. Efficacy

The efficacy of NEXIUM was reviewed according to the endoscopic findings and data of subjective symptoms.

(1) Endoscopic findings
1) The number of patients who underwent endoscopy during the period between the start of the maintenance therapy and the end of the observation period was 105 (21.2%). As the number of patients in whom recurrent RE was confirmed on endoscopy was 14 among them, the non-recurrent rate was 86.7% (91/105).
2) Endoscopic findings of the 105 patients who underwent endoscopy were classified by Los Angeles classification: Grade O (N/M) 91 patients (86.7%), Grade A/B 14 patients (13.3%) and Grade C/D 0 patient; refractory RE was not observed in these patients.
3) While there was no patient who had recurrent RE in 10 patients given NEXIUM unit dose 10 mg at the start of the maintenance therapy, the non-recurrent rate in 95 patients given NEXIUM unit dose 20 mg at the start of the maintenance therapy was transitional: 95.7% at Week 4, 90.5% at Week 12, and 82.5% at Week 24 after the maintenance therapy was started. The non-recurrence rates between patient demographic factors and treatment factors were reviewed. There were no remarkable findings in the data, and there was no significant difference in the recurrence rates between the 10 mg dose group and the 20 mg dose group ($p=0.3516$).

(2) Subjective symptoms
1) The improvement rates of subjective symptoms were as follows: heartburn 90.8% (317/349), acid regurgitation into the mouth 91.3% (209/229), epigastric pain 89.8% (168/187), eructation 85.7% (174/203), nausea 92.2% (95/103), vomiting 81.0% (17/21), swallowing difficult 85.4%

(41/48), gastric discomfort (stomach heavy feeling) 85.7% (216/258), inappetence 87.9% (94/107) and other symptoms 77.8% (14/18).
2) The resolution rates of subjective symptoms were as follows: heartburn 79.4% (277/349), acid regurgitation into the mouth 83.8% (192/229), epigastric pain 85.0% (159/187), eructation 76.4% (155/203), nausea 87.4% (90/103), vomiting 76.2% (16/21), swallowing difficult 77.1% (37/48), gastric discomfort (stomach heavy feeling) 78.2% (197/252), inappetence 85.0% (91/107) and other symptoms 72.2% (13/18).
3) According to the data concerning the change of the severity of each subjective symptom, all subjective symptoms improved after the start of the maintenance therapy, and the symptoms were no longer present at Week 24 of the maintenance therapy in 83.8% of heartburn, 86.5% of eructation, 87.5% of gastric discomfort (stomach heavy feeling), 81.0% of the symptoms of bloating and abdominal discomfort, and at least 90% of other subjective symptoms.