Japan CEI Protocol

Drug Substance esomeprazole (NEXIUM)

First edition

Revised on

NEXIUM Capsule
Clinical Experience Investigation Protocol

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1. OBJECTIVE

The objective of this investigation is to collect the following data in patients given Nexium capsules (Nexium) for standard post-marketing use.

1. Development of adverse drug reactions (ADRs) unexpected from "Precautions for Use" of Nexium JPI

2. Development of ADRs

3. Factors which may impact safety and efficacy of Nexium

2. TARGET NUMBER OF PATIENTS AND ITS RATIONALE

Target number of patients: 3000

Rationale: The number of 3000 was set to detect more than one report of an ADR, the true frequency of which is 0.1 % or higher, with 95 % probability.

The minimum target number of patients with each patient population, i.e. gastric ulcer, duodenal ulcer, reflux oesophagitis, non-erosive reflux disease who will be enrolled to the CEI was set according to the post-marketing clinical data of omeprazole and clinical study data of esomeprazole. The number of patients to be enrolled for each patient population and its rationale are as follows:

Minimum target number of patients	**Rationale**
Gastric ulcer: 106 patients	Assuming the true cure rate to be 92.5% from omeprazole post-marketing clinical data, the minimum number of patients of this population required for the investigation is approximately 106 to estimate the cure rate with the precision to show the 95% two-sided confidence interval of the observed cure rate to be included within 92.5 ±5%.
Duodenal ulcer: 63 patients	Assuming the true cure rate to be 95.7% from omeprazole post-marketing clinical data, the minimum number of patients of this population required for the investigation is approximately 63 to estimate the cure rate with the precision to show 95% two-sided confidence interval of the observed cure rate to be 95.7± 5%.
Reflux oesophagitis: 170 patients	Assuming the true cure rate to be 87.3% from the data from Nexium clinical study (Study D961H00002), the minimum number of patients of this population required for the investigation is approximately 170 to estimate the cure rate with the precision to show 95% two-sided confidence interval of the observed cure rate

	to be 87.3± 5%.
Non-erosive reflux disease: 149 patients	The true complete resolution rate of heartburn was assumed to be 32.3% from omeprazole post-marketing clinical data. If the complete resolution rate of heartburn was estimated from the same number of patients with gastric ulcer, duodenal ulcer or reflux oesophagitis using the assumed rate, the standard error of the rate would be approximately 1.5 time, so the range of the precision for the estimation was set to be ±7.5% (=5% × 1.5). The minimum number of patients of this population required for the investigation is approximately 149 to estimate the resolution rate with the precision to show the 95% two-sided confidence interval of the observed resolution rate to be included within 32.3±7.5 %.

As Zollinger-Ellison syndrome and anastomotic ulcer are rare diseases, the target number of patients with each disease is one or more, possibly more than one. When conduct of CEI is requested to a physician, it is also requested to give priority to enroll a patient with Zollinger-Ellison syndrome or anastomotic ulcer at the time when Nexium is prescribed to a patient of either of the population.

3. PATIENTS TO BE ENROLLED

Patients who have been prescribed Nexium for “gastric ulcer”, “duodenal ulcer”, “anastomotic ulcer”, “reflux oesophagitis”, “non-erosive reflux disease”, or “Zollinger-Ellison syndrome”, which are the indications of Nexium.

4. OBSERVATION PERIOD

Patients with gastric ulcer, anastomotic ulcer or Zollinger-Ellison syndrome: 8 weeks

Patients with duodenal ulcer: 6 weeks

Patients with reflux oesophagitis: 8 weeks

Patients with non-erosive reflux disease: 4 weeks

5. NUMBER OF INVESTIGATION SITES WHERE THE INVESTIGATION WILL BE CONDUCTED

Approximately 600 sites, the majority of which are the gastroenterological medicine departments

6. METHOD

1. AZKK Medical Representatives (MRs) explain the objective, target patients and methods of this CEI to the physicians in charge of the CEI at the medical institutions, and request the head of each medical institution to join the CEI. Written contract has to be concluded prior to the start of the CEI.

2. Method of the CEI is central registration. After the contract is concluded, the MR in charge of the investigation site sends Case Registration Forms and CRFs to the physician in charge of the CEI.

3. The physician in charge of the CEI enters relevant information into the Case Registration Form after a patient starts treatment with Nexium. The physician enters his/her signature on the Form, and sends to "CEI Central Registration Centre" by fax within 14 days after Nexium is started (N.B. the first day of the treatment is Day 1).

4. After the registration is completed, the MR communicates the completion of the case registration to the physician in charge of the CEI.

5. The physician in charge of the CEI follows up the patient according to the "4. Observation period" above. The physician enters data on the patient in the CRF within four weeks after the observation period is finished, and hands the CRF to the MR.

7. INVESTIGATION PERIOD

Registration period: September 2011 (launch date) - March 2013

Investigation period: September 2011 (launch date) - May 2013

8. DATA TO BE COLLECTED

1. Information required for patient identification
   Patient ID Number

2. Patient demography data
age, sex, target disease (main lesion), in-patient/out-patient classification, height, weight, smoking history, drinking habits, duration of the disease from the first onset, Helicobacter pylori infection test result, allergy (yes/no), CYP2C19 gene polymorphism status, past medical history, concurrent disease (yes/no) (if yes, disease name), previous treatment for the target disease (drugs given within four weeks before administration of Nexium) (yes/no) (if yes, drug name and administration route)

3. Pregnancy during the observation period (yes/no) (if yes, expected delivery date)

4. Nexium administration
Nexium start date, unit dose, number of daily doses; When dose was changed, unit dose and number of daily doses after the change, date of the dose change, and reason of the dose change; whether Nexium was continued or stopped, (the most recent administration date when Nexium was continued, and the last administration date and reason of discontinuation when Nexium was discontinued)

5. Administration of concomitant drugs
Whether there were concomitant drugs during Nexium administration period (if yes, drug name, administration route, and indication; and daily dose and the administration period in patients who experience any adverse event)

6. Concomitant therapy (other than drugs)
Whether there was concomitant therapy during Nexium administration period (if yes, name and purpose of the treatment; and the period of the therapy in patients who experience any adverse event)

7. Clinical course

- In patients with gastric ulcer, duodenal ulcer or anastomotic ulcer:
  Following data are collected at baseline, and when the observation period is completed or when Nexium is discontinued:
  Endoscopic findings (yes/no) (if yes, date of the endoscopy, maximum ulcer base diameter, Sakita-Miwa Classification, area of the lesion), date of medical interview, severities of subjective symptoms such as epigastric pain, anorexia, bloating, heartburn, nausea, vomiting, and eructation.

- In patients with reflux oesophagitis, or non-erosive reflux disease:
  Following data are collected at baseline, and when the observation period is completed or when Nexium is discontinued:
  Endoscopic findings (yes/no) (if yes, date of the endoscopy and Los Angeles Classification (Hoshihara's modification)), date of medical interview, severities of subjective symptoms* such as heartburn, acid regurgitation into mouth, epigastric pain, eructation, nausea, vomiting, swallowing difficult, gastric discomfort (heavy stomach) and anorexia, and frequency of heartburn

– In patients with Zollinger-Ellison syndrome
  Following data are collected at baseline, and when the observation period is completed or when Nexium is discontinued:
  Endoscopic findings (yes/no) (if yes, date of the endoscopy, the number of ulcer(s), maximum ulcer base diameter, Sakita-Miwa Classification, and area of the lesion), test dates and data of basic gastric-acid volume and serum gastrin, date of medical interview, severities of subjective symptoms* such as epigastric pain, anorexia, bloating, heartburn, nausea, vomiting, eructation, and diarrhoea

* Severity is classified as below:

Mild (patients can endure subjective signs and symptoms)

Moderate (having discomfort which may interrupt ADL)

Severe (activities of daily life (ADLs) are totally interrupted)

8. Adverse event

All AEs* during the observation period: AE term, outcome, date of outcome, seriousness**, causality with Nexium, causality factors other than Nexium, and laboratory test data related to AE(s) (test items, reference range of the investigation site, date, and data)

Additional information required for AEs of following criteria:

– Serious adverse event: Case narrative and causality comment

– Adverse event with fatal outcome: date of death, cause of death, causality assessment between Nexium and death, autopsy (yes/no) (if yes, autopsy findings)

*: At the time of development of fracture, community - acquired pneumonia, enterocolitis in association with Clostridium difficile infection, information in detail including case narrative and data of relevant tests for diagnosis is collected as much as possible.

Adverse events do not include new onset or worsening of clinical symptoms in association with the disease under investigation (main lesion) (information of endoscopic findings and subjective symptoms entered in the clinical course section of CRF) as they are efficacy endpoints.

**: Definitions of “serious” follows the ICH definitions (PFSB Notification 0328007 of 28 March 2005:

Death, Life threatening, Results in persistent or significant disability/incapacity, Requires inpatient hospitalization or prolongation of existing hospitalization, Other medically important, Congenital anomaly/birth defect

9. Others

When a patient becomes pregnant during the observation period of this CEI, the pregnancy case is to be followed up to collect data on delivery and birth.

Schedule of the observation

	Baseline	**the end of observation period*** or when Nexium is stopped****
Patient demography data	○	
Nexium administration	←	→
Administration of concomitant drugs	←	→
Concomitant therapy	←	→
Clinical course 1. Endoscopic findings* 2. Subjective symptoms:	○** ○	 ○ ○
Adverse event	←	→

*: Data are collected only from patients who are prescribed Nexium in usual clinical settings.
** Baseline endoscopic findings are the most recent endoscopic findings.
***: Data of the end of the observation period are collected on the most recent date within one week before or after the date of the end of the observation period. If the patient did not visit in the period of one week before/after the date of the end of the observation period, the data are collected on the last visit prior to the end of the observation period.
****: The date when Nexium is stopped is the date of the last visit during the treatment or the next day of the last administration of Nexium.

9. DATA ANALYSIS: ITEM AND METHOD

Definitions and analysis method of the data of the target population are entered in the Data Analysis Plan.

1. Case constitution
Number of patients enrolled in the investigation, Number of CRFs collected, Number of safety evaluable patients, Number of efficacy evaluable patients, Number of excluded patients and reason of the exclusion

2. Patient demography
Age, sex, BMI, in-patient/out-patient classification, smoking history, drinking habits, target disease (main lesion), disease period, allergy (yes/no), Helicobacter pylori infection test result, CYP2C19 gene polymorphism status, baseline severity, past medical history, concurrent disease (liver disorder, renal disorder, or others)

3. Treatment
Nexium unit dose, Nexium daily dose, previous treatment for the target disease (main lesion) (yes/no and class of the drug), concomitant drug(s) (yes/no and class of the drug* (s)), concomitant therapy (yes/no and class of the therapy)

*: including concomitant clopidogrel

4. Safety

- Development of ADR/infections sorted by SOC

- Development of ADR/infections sorted by patient demography and by treatment
  Development of ADR/infections is confirmed by patient demography and by treatment to discuss factors which may impact to safety.
  Impact of concomitant drugs especially concomitant clopidogrel is to be confirmed.

- Development of serious adverse events sorted by SOC

- Development of the AEs of fracture, community acquired pneumonia, or enterocolitis in association with clostridium difficile infection

5. Efficacy

- Cure rate on endoscopy
  In patients having endoscopic findings both in the baseline period and after Nexium is started, the percentage of patients whose cure of the target diseases has been confirmed on endoscopy (S1 or S2 in peptic ulcer patients and Grade N or M in reflux oesophagitis patients).

- Improvement rate of subjective symptoms
  Percentage of patients whose subjective symptoms improved after Nexium is started compared to baseline data

- Change of severities of individual subjective symptoms

- Improvement rate of frequency of heartburn
  In patients with reflux oesophagitis and non-erosive reflux disease, percentage

of patients whose subjective symptom of heartburn improved after Nexium is started compared to baseline.

10. ORGANISATION TO CONDUCT THE CEI

The organisation to conduct the CEI is same as that in Attachment 2 to PMS Basic Plan.

11. ORGANISATIONS TO WHICH THE OPERATIONS ARE TO BE OUTSOURCED, AND SCOPE OF THE CONTRACT

Name:

Address:

Scope of the contract:
Operations specified in the contract of Post-marketing surveillance operations; request and contract of the investigation to/with medical institutions, prompt enrollment of patients, CRF collection and follow-up investigation, progress management

Name:

Address:

Scope of the contract:
Reception of patient enrollment, and operations of data management (data entry, CRF check/data lock, and request of re-investigation, database lock, and dataset compilation)

12. OTHER REQUIREMENTS

1. Revision of the protocol
   Following information is always examined during the investigation; progress of the CEI, number of patients who discontinued the CEI, onsets of serious unexpected ADRs, large increase in the incidence of a specific ADR, and validity of the investigation items. The CEI protocol is to be reviewed and revised when necessary. When a partial revision of "Dosage and Administration" or "Indication" is approved during the CEI period (other than new establishment of the re-examination period), necessity of the revision of the CEI protocol is examined, and the document is reviewed as required.

2. Process when any issue or query is provided
   Necessity of additional Specific Clinical Experience Investigation (S-CEI) or post-

marketing clinical study is examined to detect or identify any factors of ADRs, or to verify the estimation obtained after data analysis of the CEI if there is any of followings: a significant ADR which is not expected from “Precautions for Use” of Nexium JPI is suggested, frequency of an ADR has significantly increased, there is a safety or efficacy issue compared to the data before marketing, or development of ADRs of a different nature is suggested.