Appendix1

Japan S-CEI Protocol

Drug Substance esomeprazole (NEXIUM)

First edition

Revised on

NEXIUM Capsule, NEXIUM granules for suspension (sachet) Protocol of Specific Clinical Experience Investigation in Children

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1. OBJECTIVE

The objective of this investigation is to collect the following data in pediatric patients given Nexium capsules or Nexium granules for suspension (sachet) (both combined to be referred to as 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. Efficacy

2. SAFETY SPECIFICATION TOPICS

Pancytopenia, Agranulocytosis, Platelets decreased, Shock, Anaphylaxis, Hepatic disorder (Hepatitis fulminant, Hepatic function disorder, Jaundice, Hepatitis, Hepatic failure), Severe skin disorder including Toxic Epidermal Necrolysis, Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and Erythema multiforme, Interstitial nephritis, Interstitial pneumonia, Rhabdomyolysis, Hyponatraemia, Confusional state, Haemolytic anaemia, Visual impairment, Acute kidney injury, Fracture, Gastroenteric infection due to clostridium difficile, and Pneumonia

3. OUTLINE OF CEI (DRAFT)

3.1 Target number of patients and its rationale

Target number of patients: 200 (target number of registration)

Rationale for the sample size:

Although the safety profile of Nexium observed in the Japanese clinical studies is similar to the profile observed in adult Japanese, and the safety data in Japanese pediatric patients are supported by overseas studies and post-marketing data in adults and children in Japan, the safety and efficacy data from Japanese pediatric patients is limited due to the small number of Japanese children (50 patients) enrolled in the clinical study in Japan. Therefore, it was considered necessary to conduct this investigation to confirm safety and efficacy of Nexium in Japanese patients. Based on the information from the database of Japan Medical Data Center and the result of the other similar products' Clinical Experience Investigation, it is expected that the number of pediatric patients indicated for Nexium, among those with acid-related diseases, is limited. In consequence, based on the feasibility, the target number of patients was defined as 200.

3.2 Patients to be enrolled

Patients who satisfy both of the following criteria

- Patients aged 1(inclusive) to 15 (exclusive) years
- Patients who have been prescribed Nexium for the first time for “gastric ulcer”, “duodenal ulcer”, “anastomotic ulcer”, “reflux oesophagitis”, “non-erosive reflux disease”, or “Zollinger-Ellison syndrome”, which are the indications of Nexium.

3.3 Observation period

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

Patients with duodenal ulcer: 6 weeks

Patients with non-erosive reflux disease: 4 weeks

3.4 Number of investigation sites where the investigation will be conducted

Approximately 40 sites, the majority of which are the pediatric department, internal medicine department and gastroenterological medicine departments

3.5 Method

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

2. Method of this S-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 this S-CEI.

3. The physician in charge of this S-CEI enters relevant information into the Case Registration Form after a patient starts treatment with Nexium who meet the definitions specified in section “3.2 target patient population”. The physician enters his/her signature on the Form, and sends to “S-CEI 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 this S-CEI.

5. The physician in charge of this S-CEI follows up the patient according to the “3.3. Observation period” above. The physician enters data on the patient in the CRF

within four weeks after the observation period is finished, affix their signatures or their names and seals on the CRFs, and hand them to the MRs in charge.

3.6 Investigation period

Registration period: May 2018 - January 2020

Investigation period: May 2018 - March 2020

3.7 Data to be collected

1. Information required for patient identification
   Patient ID Number

2. Patient demography data
   age, sex, target disease (main lesion) and pathogenesis, in-patient/out-patient classification, duration of the disease from the first onset, height, weight, , Helicobacter pylori infection test result, allergy (yes/no), CYP2C19 gene polymorphism status,

3. Pregnancy during the observation period (yes/no) (if yes, expected delivery date) (only for female after menophania and of child-bearing potential)

4. Past medical history, concurrent disease (yes/no) (if yes, disease name)

5. Previous treatment for the target disease (main lesion) (drugs given within four weeks before administration of Nexium) (yes/no) (if yes, drug name and administration route)

6. Nexium administration
   Nexium start date, Product name, unit dose, number of daily doses; When product name or dose was changed, unit dose and number of daily doses after the change, date of the product name or dose change, and reason of the product name or 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), compliance of Nexium intake

7. 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)

8. 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)

9. Subjective and objective symptoms

Subjective/objective symptoms

Date of medical interview, and yes/no and severity** of symptoms* of heartburn, regurgitation, epigastric pain, upper abdominal discomfort

*: The following questions will be asked about the symptoms

Looking back your condition in the past one week, did you have the following symptoms?

Heartburn: Did you have a burning feeling, rising from the stomach or lower part of the chest towards the neck?

Regurgitation: Did you have flow or sour or bitter fluid in to mouth?

Epigastric pain: Did you have central upper abdominal pain?

Upper abdominal discomfort: Did you have abdominal discomfort (abdominal distension, etc.)?

**: Severity is defined as follows.

0: I did not have this symptom

1: I had this symptom but I tolerated it easily

2: I had this symptom with discomfort sufficient to cause interference with normal activities (eating, schoolwork or sleeping etc.)

3: I was not able to perform normal activities (eating, schoolwork or sleeping etc.)

Endoscopic findings

Endoscopic findings (yes/no) (if yes, date of the endoscopy, date of endoscopy, endoscopic assessment*)

*: For the endoscopic assessment, the physician in charge of this S-CEI judges either “Resolved” or “Unresolved” based on the Sakita-Miwa Classification (Sakita et al 1970) for gastric ulcer, duodenal ulcer, and anastomotic ulcer, and based on the Los Angeles Classification (Hoshihara’s modification) (Hoshihara 2004) for reflux esophagitis and non-erosive gastroesophageal reflux disease.

pH, other examinations

10. 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)

Adverse events do not include new onset or worsening of clinical symptoms in association with the disease under investigation (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

11. Others

When a patient becomes pregnant during the observation period of this S-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[1] or when Nexium is stopped[2]**
Patient demography data	○	
Nexium administration	←	→
Administration of concomitant drugs	←	→
Concomitant therapy	←	→
Clinical course Subjective/objective symptoms Endoscopic findings[3]	 ○ ○	 ○ ○
Adverse event	←	→

1. 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 defined for the target disease (main lesion) under investigation. 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.
2. 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.
3. Data are collected only from patients who are prescribed Nexium in usual clinical settings.

3.8 Data analysis: item and method

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

1. Items on patient subsets analysed

   1) safety analysis

   2) efficacy analysis

2. Items and methods for analysis

   1) Case constitution
   Number of patients enrolled in the investigation, Number of CRFs collected, Number of patients for safety analysis, Number of patients for efficacy analysis, Number of excluded patients and reason of the exclusion

   2) Patient demography
   Age, sex, BMI, in-patient/out-patient classification, target disease (main lesion), disease period, allergy (yes/no), Helicobacter pylori infection test result, CYP2C19

gene polymorphism status, past medical history, concurrent disease (liver disorder, renal disorder, or others)

3) Treatment

Nexium product name, 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)

4) Safety

1) Development of ADR sorted by unexpected from "Precautions for Use" of Nexium JPI

2) Development of ADR/infections sorted by SOC

3) Development of ADR/infections sorted by patient demography and by treatment

4) Development of serious adverse events sorted by SOC

5) Efficacy

1) Rage of improvement/worsening of subjective/objective symptoms

Proportion of patients who experienced improvement/worsening of subjective/objective symptoms before and after initiation of Nexium treatment

2) 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 (main lesion) has been confirmed on endoscopy (S1 or S2 in peptic ulcer patients and Grade N or M in reflux oesophagitis patients).

3.9 Organisation to conduct this S-CEI

The organisation to conduct this S-CEI is same as that in Attachment 2 to Risk Management Plan.

3.10 Organisations to which the operations are to be outsourced, and scope of the contract

Name: [redacted]

Address: [redacted]

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: [redacted]

Address: [redacted]

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)

Name: [redacted]

Address: [redacted]

Scope of the contract:
Contract processing service with medical institution

4. ADDITIONAL MEASURES WHICH MAY BE REQUIRED BASED ON RESULTS OF PHARMACOVIGILANCE ACTIVITIES, AND GO/NO-GO CRITERIA OF THE MEASURE

At each milestone, the risk management plan will be reviewed.

The review includes:

・Examination on necessity to revise the investigation protocol including presence/absence of new safety topic.

・Examination on necessity to develop a risk minimisation plan for the new safety topic.

5. TIMING OF ASSESSING IMPLEMENTATION STATUS AND RESULTS, OR MILESTONES, AND ITS RATIONALES

・At the time of the J-PBRER submission, to regularly review the safety information and efficacy information.

・At the time of the final report, to comprehensively review the safety information and efficacy information.

6. OTHER REQUIREMENTS

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

7. REFERENCES

Sakita et al 1970
Takao SAKITA, Tsuyoshi MIWA. Endoscopic diagnosis of malignant tumour – for early diagnosis -. Jpn. J. Gastroenterol 1970;67(11) 984-9

Hoshihara 2004
Yoshio HOSHIHARA. Progress of clinical examination and diagnosis – endoscopic diagnosis. Jpn. J. Clin. Med 2004;62(8):1459-64