Japan S-CEI Protocol

Drug substance esomeprazole (NEXIUM)

First edition

NEXIUM Capsule Specific Clinical Experience Investigation to investigate treatment response to NEXIUM in patients with reflux esophagitis

- Justification of Esomeprazole in Acid Related Disease for Reflux Symptom Healing based on Patient Clinical Outcomes -

TABLE OF CONTENTS **PAGE**

1. OBJECTIVES

The objective of this investigation is to collect following data in patients given NEXIUM capsule (NEXIUM) in usual post-marketing use.

Primary objective

To investigate treatment response to NEXIUM in patients with reflux esophagitis (RE).

Secondary objectives

To investigate following items in patients with RE:

1. Patient satisfactory level of the treatment for RE
2. Health-related quality of life (HRQOL)
3. Severity and frequency of RE symptoms reported by physicians
4. Endoscopic healing rate
5. Development of ADRs

2. TARGET NUMBER OF PATIENTS AND ITS RATIONALE

Target number of patients: 1,500 (patients to be registered to the S-CEI)

Rationale:

The number of patients is calculated as the number of samples required to presume the rate of patients satisfied with the four-week treatment after the start of NEXIUM based on the data below.

In the previous studies in which response to the therapy was assessed using GerdQ in patients with RE[1),2)], response to the treatment with NEXIUM was observed in about 70-85% of the patients. According to the data, the rate of patients who will achieve response to the treatment is assumed to be 80% in this investigation.

The number of patients required for analysis is calculated to be 683 to ensure the width of the 95% Confidence Interval would be within ±3%.

In view of the data of previous NEXIUM CEI/S-CEI, the rate of patients withdrawn from the investigation due to various factors, and the rate of patients from whom data of the response to the treatment can be collected without fail are estimated to be 30% and 70%, respectively. Taking into account these figures, it has been calculated that enrollment of 1,394 patients is required for this S-CEI.

Accordingly, the number of patients required in this S-CEI was considered to be 1,500.

3. PATIENTS TO BE ENROLLED

Since the target patient population of the S-CEI is symptomatic RE patients, the patients fulfilling the inclusion criteria and not the exclusion criteria shown below will be enrolled as the subjects of this investigation.

Inclusion criteria

Patients to be enrolled in this S-CEI must fulfill all the criteria below at the start of the treatment with NEXIUM.

1. Aged at least 20 years.
2. Patients who has a current or past history of clinically diagnosed RE
3. Patients whose answers in the baseline GerdQ include "2-3 days" or "4-7 days" in at least one of the questions Nos1, 2, 5 and 6.
4. Patients to whom NEXIUM 20 mg once daily is to be administered for RE
5. Patients from whom written consent has been obtained.

Exclusion criteria

Patients must not enter the investigation if any of the following exclusion criteria are fulfilled at the start of the treatment with NEXIUM:

1. Patients whose ability to follow instructions are suspected to be low by physicians
2. Patients with a past history of hypersensitivity to the ingredients of NEXIUM.
3. Patients receiving atazanavir sulfate or rilpivirine hydrochloride
4. Patients who have received NEXIUM within the past eight weeks for treatment of RE

4. OBSERVATION PERIOD

8 weeks

5. NUMBER OF INVESTIGATION SITES (HOSPITAL DEPARTMENTS)

Approximately 400 sites, majority of which are the internal medicine or gastrointestinal medicine departments

6. METHOD

1. AZKK Medical Representatives (MRs) explain objectives, the target patient and the method of this S-CEI to the physicians in charge of the S-CEI at the medical institutions which have issued prescriptions of NEXIUM, and request conduct of the S-CEI to the head of the medical institutions. Written contract has to be concluded prior to the start of the S-CEI.

2. Method of the S-CEI is central registration. After the contract is concluded, the MR in charge of the investigation site sends Case Registration Forms, CRFs, Forms of Questionnaires (GerdQ, patient satisfaction questionnaire and SF-8^{TM}-Japanese version) and information materials for RE to the physician in charge of the S-CEI.

3. The physician in charge of the S-CEI explains the investigation with the informed consent form to the patients eligible to the investigation (See 3. above), and obtains written consent from them (however, patients may not be eligible according to the result of GerdQ even if the consent is obtained from them).

4. After the consent is obtained, the physician in charge of the S-CEI hands the first questionnaire to the individual patients, and confirms the result of GerdQ. When the patient fulfills the criteria of "3. Patients to be enrolled", the physician in charge of the S-CEI recommends the patients to enter all replies in the first questionnaires, and hands the patient information materials for RE. The first questionnaires filled out by the patient are promptly collected at the investigation site.

5. The physician in charge of the S-CEI enters relevant information into the Case Registration Form with his/her signature, and sends to “S-CEI Registration Centre” by fax within 14 days after the NEXIUM is started (N.B. the first day of the treatment is Day 1).

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

7. The physician in charge of the S-CEI recommends the patients to fill out the second and the third questionnaire forms on Week 4 and Week 8 of the treatment. The relevant questionnaires filled out by the patient are promptly collected at the investigation site.

8. The physician in charge of the S-CEI follows up the patient according to the “4. Observation period” above. The physician enters data of the patient in CRF within four weeks after the observation period is finished, and hands the CRF to the MR.

7. INVESTIGATION PERIOD

Registration period: 01 July 2015 to 30 June 2016 (one year)

Investigation period: 01 July 2015 to 31 August 2016 (one year and two months)

The registration is finished when the number of patients enrolled to the investigation reaches the target number of patients.

8. DATA TO BE COLLECTED

1. Information required for patient identification

   Patient ID Number

2. Patient (baseline) demography

   Age, sex, inpatient/outpatient classification, height, weight, smoking history, drinking habits, duration of the disease from the first onset, *Helicobacter pylori* infection test result, allergy (yes/no)

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

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

5. Previous treatment for RE (drugs given within four weeks before administration of NEXIUM) (yes/no) (if yes, drug name and administration route)

6. NEXIUM administration

   NEXIUM start date, reason of the use, unit dose, and number of daily doses

   Changed unit dose/number of daily dose when the treatment regimen was changed, date of the change, and reason of the change

   NEXIUM was continued or discontinued (the most recent prescription date when NEXIUM was continued, and the last prescription date and reason of discontinuation when NEXIUM was discontinued)

7. Withdrawal of the informed consent (yes/no) (if yes, the date of the consent withdrawal)

8. Administration of concomitant drugs

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

9. Concomitant therapy (other than medication)

Therapy given during the treatment period of this investigation (yes/no) (if yes, name of therapy and purpose of therapy, and the period of the therapy in patients who experience any adverse event)

10. Clinical course

Following data are collected when treatment with NEXIUM is started, at Treatment Week 4 and Treatment Week 8, or the end of the observation period (in patients in whom NEXIUM was discontinued).

Endoscopic findings of RE (yes/no) (if yes, date of the endoscopy and Los Angeles Classification (Hoshihara's modification)),

Date of medical interview, severity* of subjective symptoms such as heartburn, acid regurgitation, epigastric pain, eructation, nausea, vomiting, dysphagia, gastric discomfort (heavy stomach) and anorexia, and frequency of heartburn.

Severity is classified as below:
Mild (Awareness of symptom, but easily tolerated)

Moderate (Discomfort sufficient to cause interference with normal activities)

Severe (Incapacitating, with inability to perform normal activities)

11. Adverse event

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

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 clinical symptoms in association with the recurrent RE included in "Findings during the treatment with NEXIUM" above (endoscopic findings and subjective symptoms) 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

12. Questionnaire collection (yes/no)

13. Questionnaire

Following data are collected in the questionnaire at the start of NEXIUM, on Treatment Week 4 and Treatment Week 8, and when the observation period is completed, or when NEXIUM was discontinued:

Questionnaire on the gastrointestinal symptoms: GerdQ[3)]

Questionnaire on NEXIUM: patient satisfaction questionnaire*

Questionnaire on health conditions: SG-8™ Japanese version[4)]

Compliance with the treatment with NEXIUM

* Patient satisfaction questionnaire is as below:

Please provide the degree of satisfaction on the current treatment for RE. (Choose one of them: extremely satisfactory, very satisfactory, satisfactory, neither satisfactory nor dissatisfactory, dissatisfactory, very dissatisfactory, or extremely dissatisfactory.)

14. Others

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

Schedule of the observation

CRF	**Baseline**	**Treatment Week 4[*1]**	**Treatment Week 8, or end of the observation period (treatment discontinued)[*2]**
Patient demography data	○		
NEXIUM administration	←	—	→
Administration of concomitant drugs	←	—	→
Concomitant therapy	←	—	→
Clinical course			
Endoscopic findings[*3]	○	○	○
Subjective symptoms	○	○	○
Adverse event	←	—	→

Questionnaire	Baseline	Treatment Week 4[*1]	Treatment Week 8 or end of the observation period (when NEXIUM is discontinued)[*2]
GerdQ	○	○	○
Patient satisfaction questionnaire	○[*4]	○	○
SF-8™ Japanese version	○	○	○
Compliance with the treatment with NEXIUM		○	○

*1: Treatment Week 4 is the period +/- 1 week of 4 weeks after NEXIUM is started.
*2: Treatment Week 8 is the period +/- 1 week of 8 weeks after NEXIUM is started. If the patient did not visit in the period of one week before or after the date of Treatment Week 8, the data are collected on the last visit prior to Treatment Week 8.
The date when NEXIUM is discontinued is the date of the last visit during the treatment or the next day of the last prescription of NEXIUM.
*3: Data are collected only from patients who are prescribed NEXIUM in usual clinical settings.
*4: Patient satisfaction questionnaire is not given to the patient who has no history of medication for RE prior to the start of NEXIUM.

9. DATA ANALYSIS: ITEM AND METHOD

Primary endpoint

The rate of patients whose answers in the GerdQ are "none" or "one day" in the questions Nos 1, 2, 5 and 6 at the end of the observation.

Secondary endpoint

Following items will be assessed:

Definitions and data analysis method of each analysis set are explained in Data Analysis Plan.

1. Case constitution

   Number of patients enrolled in the S-CEI, Number of CRFs collected, Number of questionnaire forms collected, Number of patients in the safety analysis set, Number of patients in the efficacy analysis set, Number of patients excluded from the analysis and reason of the exclusion

2. Patient demography items

   Age, sex, in-patient/out-patient classification, BMI, smoking history, drinking habits, disease period, *Helicobacter pylori* infection test result, allergy (yes/no), past medical history and concurrent disease (hepatic disorder, renal disorder, or others)

3. Treatment

NEXIUM unit dose, daily dose, compliance with the treatment, previous treatment for RE (yes/no and class of the drug), concomitant drug(s) (yes/no and class of the drug* (s)), and concomitant therapy (yes/no and category of the therapy)

4. Efficacy

1) Treatment response to NEXIUM

The rate of patients whose answers in the GerdQ are "none" or "one day" in the questions Nos 1, 2, 5 and 6 at the time of Treatment Week 4 and 8.

2) Patient satisfaction for the treatment

The rate of the patients whose answers in the patient satisfaction questionnaire are "satisfactory" at the time of Treatment Week 4 and 8 and at the end of the observation.

3) Health-related quality of life

Mean score of SF-8^{TM} Japanese version at the time of Treatment Week 4 and 8 and at the end of the observation.

4) Improvement rate of subjective symptoms

The rate of patients whose subjective symptoms (heartburn, acid regurgitation in the mouth, epigastric pain, eructation, nausea, vomiting, dysphagia, gastric discomfort (heavy stomach) and anorexia) improved at the time of Treatment Week 4 and 8 and at the end of the observation.

5) Change of severity of individual subjective symptoms

6) Improvement rate of frequency of heartburn

7) Endoscopic healing rate

Rate of patients who achieved Grade N or M of Los Angeles classification on endoscopy

5. Safety

1) Development of ADR/infection sorted by SOC

2) Development of serious adverse event sorted by SOC

10. AZKK ORGANISATION TO CONDUCT THE S-CEI

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

The preparation and revision of the S-CEI will be discussed at the independent IRB.

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

Contract companies

Company 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

Company name:
Address:

Scope of the contract:
Handling of contract with medical institutions, Handling of patient enrollment, and operations of data management (e.g. data entry, CRF check/data lock, and request of follow-up investigation, database lock, and dataset compilation)

12. MEDICAL ADVISORS

Name and affiliation of advisor A:

Name and affiliation of advisor B:

Name and affiliation of advisor C:

Major role of the medical advisors

Give guidance and advice as medical experts to the sponsor of the S-CEI on planning and compiling of the data collected from the investigation.

13. OTHER REQUIRED ITEMS

1. Revision of the protocol

Following information is always captured during the investigation; progress of S-CEI, number of patients withdrawn, onset of serious unexpected ADRs, large increase of the incidence of specific ADRs, and validness of the investigation items. The S-CEI protocol is to be reviewed and revised when it is necessary.

When an application for partial revision of "Dosage and Administration" or "Indication" is approved during the S-CEI period (other than new establishment of the re-examination period), necessity of the revision of the S-CEI protocol is examined, and the document is revised as required.

2. Process when any issue or query is observed

Necessity of additional S-CEI or a 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 S-CEI if there is any of the followings: a significant ADR which is not expected from "Precautions for Use" of the 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.

14. REFERENCE

1. Shinichi Ishihara, Treatment of reflux esophagitis by a clinician - Efficacy rate and symptom improvement effects of esomeprazole, Pharma Medica.2012; 30: 77-83.

2. Haruhiko Nagami, Study of symptoms disappearance rate and efficacy rate by switching to esomeprazole – The relationship between treatment effects and patient background factor of elderly patient with GERD. Therapeutic Research. 2012; 33: 265-77.

3. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther. 2009; 30: 1030-38.

4. Shunichi Fukuhara, Yoshimi Suzukamo, Instruments for measuring Health - related Quality of Life - SF-8 and SF-36. Strides of Medicine. 2005; 213: 133-6.

ATTACHMENT

(a) Contract template (draft)

(b) Specific Clinical Experience Investigation guidance (draft)

(c) Specific Clinical Experience Investigation patient enrollment form (draft)

(d) Specific Clinical Experience Investigation CRF (draft)

(e) Questionnaires (draft): 1st (baseline), 2nd (Treatment Week 4), 3rd (Treatment Week 8 or at the last prescription of the discontinuation case)

(f) Master Informed Consent Form (draft)