Japan S-CEI Protocol

Drug substance esomeprazole (NEXIUM)

First edition

Current edition

NEXIUM® Capsule

Protocol of Specific Clinical Experience Investigation Maintenance Therapy for Repeatedly Recurring/Relapsing Reflux Oesophagitis

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1. OBJECTIVE

The objective of this investigation is to collect following data in patients given NEXIUM capsule (NEXIUM) in usual post-marketing use as the maintenance therapy for repeatedly recurring/relapsing reflux oesophagitis.

(1) Efficacy in the maintenance therapy (non-recurrence rate of reflux oesophagitis)

(2) ADR development in the maintenance therapy

(3) Factors which may impact safety and efficacy of the maintenance therapy (non-recurrence rate of reflux oesophagitis) of NEXIUM

(4) Efficacy and safety in patients given the maintenance therapy dose of 20 mg

2. TARGET NUMBER OF PATIENTS AND ITS RATIONALE

Target number of patients: 600 (patients to be registered to the S-CEI)

Rationale:
In the S-CEI, the estimated number of patients who will receive the maintenance therapy for six months is set as at least 300. In the long-term investigation of Omepral maintenance therapy for reflux oesophagitis, approximately 75 % of the enrolled patients were followed up for longer than six months. The target number of patients of this S-CEI is determined as 600 to surely collect data of patients for six months of the administration period assuming that approximately 50 % of these patients are to be given NEXIUM for longer than six months.

In the long-term investigation of Omepral maintenance therapy for reflux oesophagitis, approximately 50 % of the enrolled patients were given Omepral 20 mg/day as the maintenance therapy. In view of this previous data, estimated number of patients who are to be given NEXIUM 20 mg/day for the maintenance therapy is approximately 300.

3. PATIENTS TO BE ENROLLED

Patients with repeatedly recurring/relapsing reflux oesophagitis who will be given NEXIUM for the first time as a maintenance therapy.

(Patients who had a past history of treatment with NEXIUM as the initial treatment for reflux oesophagitis are eligible.)

Exclusion criteria:

(1) Patients who have reflux oesophagitis at the time of starting NEXIUM as the maintenance therapy (Endoscopic classification is Grade A, Grade B, Grade C or Grade D of Los Angeles Classification (Hoshihara's modification))

(2) Patients who had a past history of the maintenance therapy for repeatedly recurring/relapsing reflux oesophagitis with NEXIUM

4. OBSERVATION PERIOD

Six months

When treatment with NEXIUM was completed/discontinued within six months or a patient stopped visiting his/her physician, the date and the reason are confirmed, and the period until the date is determined as the observation period.

5. NUMBER OF INVESTIGATION SITES WHERE THE INVESTIGATION IS CONDUCTED

Approx 120 sites, majority of which is the gastroenterological medicine department

6. METHODS

(1) AZKK Medical Representatives (MRs) explain objectives, target patients and methods of this S-CEI to the physicians in charge of the S-CEI at the medical institutions which decided to issue 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 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 and CRFs to the physician in charge of the S-CEI.

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

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

(5) 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:

Investigation period:

8. DATA TO BE COLLECTED

(1) Information required for patient identification

Patient ID Number

(2) Patient (baseline) demography data

Age, sex, in-patient/out-patient classification, height, weight, smoking history, drinking habits, *Helicobacter pylori* infection test result, allergy (yes/no), status of CYP2C19 polymorphism (yes/no)

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

(4) Previous medical history and concomitant disease (other than reflux oesophagitis) (yes/no) (if yes, the disease term(s))

(5) History of reflux oesophagitis and previous treatment for reflux oesophagitis prior to the maintenance therapy with NEXIUM

(6) NEXIUM administration

NEXIUM start date for the maintenance therapy, unit dose, number of daily doses

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

Drug compliance

Whether NEXIUM was continued or discontinued,
(the most recent administration date if NEXIUM was continued, the last administration date and reason of discontinuation if NEXIUM was discontinued)

(7) Administration of concomitant drugs

Concomitant drug during the S-CEI (yes/no), (if yes, drug name, administration route, and indication)

Daily dose and administration period in AE cases

(8) Concomitant therapy (other than drugs)

Concomitant therapy conducted during the S-CEI (yes/no), (if yes, name of the therapy, its purpose, and the period of the therapy in AE cases)

(9) Clinical course

Endoscopic findings (yes/no), (if yes, date of endoscopy, Los Angeles Classification (Hoshihara's modification)), subjective symptoms (yes/no) (if yes, date when the information was collected, yes/no and severity* of the symptoms of heartburn, acid regurgitation in mouth, epigastric pain, eructation, nausea, vomiting, swallowing difficulty, gastric discomfort (heavy stomach) and anorexia)

* 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)

(10) Adverse event

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

Information of serious adverse events includes case narrative and causality comment of the events

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

*: At the time of development of fracture, community acquired pneumonia, or enterocolitis in association with Clostridium difficile infection, information in detail including case narrative and data of relevant diagnostic tests is collected as much as possible. Adverse events do not include recurrence of reflux oesophagitis and clinical symptoms in association with the recurrence (included in the clinical course (endoscopic findings and subjective symptoms)) as they are efficacy endpoints.

**: Definitions of "serious" follows the ICH definitions (PFSB/SD 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 important medical event, 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 of delivery and birth.

Schedule of the observation

	at the start of maintenance therapy	**at the end of observation period*, or when NEXIUM is discontinued*** **
Patient demography data	○	
NEXIUM administration	←———	———→
Administration of concomitant drugs	←———	———→
Concomitant therapy	←———	———→
Clinical course 1) Endoscopic findings* 2) Subjective symptoms:	←——— ←———	———→ ———→
Laboratory test	←———	———→
Adverse event	←———	———→

* Data are collected only from patients who are prescribed NEXIUM in usual clinical settings.

** The end of the observation period is the date of the visit nearest to the end of the observation date within ± 2 weeks of the end of the observation period. If the patient did not visit in the period of two weeks before or after the end of the observation date, the date are collected on the last visit during the treatment.

*** The date when NEXIUM is discontinued 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 explained in Data Analysis Plan.

(1) Case constitution

Number of patients enrolled in the investigation, number of CRFs collected, number of patients included in the safety analysis set, number of patients included in the efficacy analysis set, patients excluded from the analysis and reason of the exclusion

(2) Patient demography

Age, sex, BMI, in-patient/out-patient classification, smoking history, drinking habits, history of previous onset and recurrence of reflux oesophagitis (total number of recurrence), allergy (yes/no), *Helicobacter pylori* infection status, status of CYP2C19 polymorphism, past medical history, concomitant disease (liver disorder, renal disorder, or others)

(3) Treatment

NEXIUM unit dose, NEXIUM daily dose, previous treatment drug for reflux oesophagitis (yes/no), concomitant drug(s)* (yes/no and class of the drug(s)), concomitant therapy (yes/no)

*: including concomitant use of clopidogrel

(4) Safety

1) The numbers and rate of ADR events sorted by SOC

2) The numbers and rate of ADR events sorted by patient demography and by treatment
The frequency of ADR is confirmed by patient demography and by treatment to discuss factors which may impact to safety
Impact of concomitant drugs to safety especially concomitant clopidogrel is to be confirmed.

3) The numbers and rate of serious adverse event

4) The numbers and rate of fracture, community acquired pneumonia, and enterocolitis in association with *clostridium difficile* infection

(5) Efficacy

1) Non-recurrence rate of reflux oesophagitis
Proportion of patients in whom reflux oesophagitis did not recur during NEXIUM maintenance therapy

2) Examination of factors which may impact non-recurrence rate of reflux oesophagitis.

3) Proportion of patients who experienced worsening of subjective symptoms
Proportion of patients who experienced worsening of subjective symptoms during the maintenance therapy with NEXIUM

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.

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

Contract companies

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, promotion of patient enrollment, CRF collection and follow-up investigation, progress management

Name:

Address:

Scope of the contract:
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. 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" of NEXIUM 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.