Prepared on 2 July 2012

Revised on 20 July 2012

Revised on 26 Sep 2012

Nexium Capsule

S-CEI for long-term use (suppression of recurrence of gastric and duodenal ulcers associated with low dose aspirin therapy)
- Protocol -

1. Objective

The objective of this investigation is to collect following data in patients given Nexium capsule (Nexium) for long term in usual-post-marketing therapy to suppress recurrence of gastric ulcer or duodenal ulcer during low dose aspirin (LDA).

(1) Efficacy in long-term use (non-recurrence rate of peptic ulcer)

(2) ADR development in long-term use

(3) Factors which may impact safety and efficacy of long-term use (non-recurrence rate of peptic ulcer) of Nexium

2. Target number of patients and its rationale

Target number of patients: 2000 (patients to be registered to the S-CEI)

Rationale:

In this S-CEI, the estimated number of patients who will receive Nexium for one year is set as more than those enrolled to the Asian phase III control study (approx 100 patients for 52 weeks) in patients continuously given LDA before approval. As the number of Japanese patients was small in the phase III study, this S-CEI will collect data from 300 patients to whom Nexium is to be administered for more than one year. The target number of patients is determined as 2000 to surely collect 300 patients with one year of the administration period assuming that approximately 10 % of these patients are to be given Nexium for more than one year.

3. Patients to be enrolled

The patients who are continuously given LDA to suppress thrombus/embolism and who will be given Nexium for the first time to suppress recurrence of gastric ulcer and duodenal ulcer.

(Patients who have previous experience of Nexium given in the treatment for gastric ulcer or duodenal ulcer can be registered to this S-CEI.)

Exclusion criteria

(1) Patients having gastric ulcer/duodenal ulcer when Nexium is started (Active phase (A1, A2) or healing phase (H1, H2) of Sakita-Miwa classification on endoscopy)

(2) Patients who had been given Nexium for suppression of recurrence of gastric ulcer/duodenal ulcer.

4. Observation period

2 years

When treatment with Nexium or LDA was completed/stopped or a patient stopped visiting the relevant physician, the date and the reason are confirmed, and the period until the date is considered as the observation period of this patient.

5. Number of investigation sites where the investigation is conducted

Approx 400 sites majority of which are internal medicine, division of cardiovascular disease, department of neurosurgery

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 the S-CEI.

(2) Method of the S-CEI is central registration. After the contract is concluded, MR in charge of the investigation site sends Case Registration Forms and CRF 1 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 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 the Nexium is started (N.B. the first day of the treatment 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 1 within four weeks after one year has passed since the treatment is started , and hands it to the MR.

(6) MR requests the physician to enter data in CRF 2 after CRF 1 is collected, when the data in CRF 1 shows that both Nexium and LDA have been continued for more than one year. The physician in charge of the S-CEI enters data of the patient in CRF 2 within four weeks after two years has passed since the treatment is started.

7. Investigation period

Registration period: Jan 2013 to Jun 2014 (1 yr 6 mon)

Investigation period: Jan 2013 to Jun 2016 (3 yr 6 mon)

8. Data to be collected

(1) Information required for patient identification
ID Number

(2) Patient demography data
age, sex, indication of LDA (disease or surgery for which suppression of thromboembolic formation is required), history of peptic ulcer (disease name, the most current onset period), in-patient/out-patient classification, height, weight, smoking habits, drinking habits, H.pylori test data (pos/neg), allergy (yes/no), CYP2C19 polymorphism

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

(4) Past history, concurrent disease (excluding peptic ulcer and indication of LDA) yes/no (if yes, disease name)

(5) Previous treatment for suppression of recurrent peptic ulcer
Drugs given within 4 weeks before Nexium (yes/no) (if yes, Name of drug, administration route, unit dose (unit), number of daily doses)

(6) Nexium administration
Nexium start date: unit dose, number of daily doses
When dose was changed, unit dose of each drug after the change, number of daily doses, date of the dose change, reason of the dose change
Compliance with Nexium
Whether Nexium was continued or stopped, (the most recent administration date if Nexium was continued, the last administration date, and reason of discontinuation if Nexium was stopped)

(7) Administration of LDA
Name of drug and daily dose (unit).
At the time of the change of the dosage and administration of the LDA, the name of the LDA, daily dose (unit), start date, dosage and administration, and reason of change

(8) Administration of concomitant drugs other than LDA
Drugs given during observation periods of this investigation (yes/no) (if yes, Name of drug, administration route, indication. Daily dose and administration period in AE cases

(9) Concomitant therapy (other than drugs)
Therapy given during observation periods of this investigation (yes/no) (if yes, name of therapy, purpose of therapy, period of the therapy in AE cases)

(10) Clinical course

Treatment Year 1:

Endoscopic findings (yes/no), (if yes, date of endoscopy, haemorrhage (yes/no), number of ulcer(s) max diameter of ulcer base,Sakita-Miwa Classification, region)

Subjective symptoms:
(date of doctor's interview, epigastric pain, anorexia, bloating, heartburn, nausea, vomiting, belch, yes/no and severity*)

* Severity is classified as below:
Mild (patients can endure subjective signs and symptoms), Moderate (having discomfort which interrupts ADL), Severe (activities of daily life (ADLs) are interrupted)

Treatment Year 2:

Endoscopic findings (yes/no), (if yes, date of endoscopy, haemorrhage (yes/no), number of ulcer(s) max diameter of ulcer base, Sakita-Miwa Classification, region),

(11) Adverse event

Terms of all AEs* in the observation period, onset date, 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)

Information of serious adverse events including 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, autopsy (yes/no) (if yes, autopsy findings)

*: At the time of development of fracture, community acquired pneumonia, enterocolitis in association with Clostridium difficile infection and microscopic colitis (collagenous colitis and lymphocytic colitis), information in detail including case narrative and data of relevant tests for diagnosis is collected as much as possible.
Adverse events do not include recurrence of gastric ulcer or duodenal ulcer or 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 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) 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

Data item \ Observation period		CRF 1 Treatment Year 1: when Nexium was started	CRF 1 Treatment Year 1: Visit after Treatment Year 1** or when Nexium is stopped***	CRF 2 Treatment Year 2: Visit after Treatment Year 2** or when Nexium is stopped**
Patient demography data		●	—	—
Nexium administration	Continued/stopped	—	●	●
	Administration	●		○
	Compliance	●		○
Administration of LDA	Continued/stopped	—	●	●
	Administration	●		○
	Compliance	●		○
Administration of concomitant drugs other than LDA		●		○
Concomitant therapy		●		○
Clinical course	Endoscopic findings* (e.g. haemorrhage yes/no)	—	●	●
	Subjective symptoms:	●	●	—
Adverse event (development condition of adverse events such as fracture)		●		●

● CRF data item

○ CRF data item to be collected in the patients who develop gastric ulcer / duodenal ulcer or any adverse event in Treatment year 2.

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

**: Data of Treatment Year 1 are collected on the most recent date within two weeks after Treatment Year 1. Data of Treatment Year 2 are collected on the most recent date within two weeks before/after Treatment Year 2. If the patient did not visit in the period of two weeks before or after Treatment Year 2, the data are collected on the last visit prior to Treatment Year 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.

9. Data analysis: item and method

Definitions and analysis method of the data of the target population are entered in 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 habits, drinking habits, Indication of LDA, history of peptic ulcer), onset period (period from the recent onset period to starting Nexium therapy, allergy (yes/no), H.pylori test data (pos/neg), genetic

polymorphism of CYP2C19, past medical history, concurrent disease (liver disorder, renal disorder, or others)

(3) Treatment
Nexium unit dose, Nexium daily dose, previous treatment to suppress recurrence of peptic ulcer (yes/no), major LDA used to the patient, LDA daily dose concomitant drug(s) (yes/no and class of the drug(s))*, concomitant therapy (yes/no)
*: including concomitant clopidogrel

(4) Safety
1) Development of ADR/infection sorted by SOC
2) ADR/infection development by patient demography data, and by treatment.
Development of ADR/infection is confirmed by patient demography and by treatment to discuss factors which may impact to safety.
3) Development of serious adverse event sorted by SOC
4) Development of fracture, community acquired pneumonia, enterocolitis in association with Clostridium difficile infection and microscopic colitis (collagenous colitis and lymphocytic colitis)
5) Cardiovascular event in patients given clopidogrel concomitantly (yes/no)

(5) Efficacy
1) Non-recurrence rate of peptic ulcer
Proportion of patients in whom peptic ulcer did not recur after treatment with Nexium
2) Examination of factors which may impact non-recurrence rate of peptic ulcer. Impact of concomitant drugs especially glucosteroid to non-recurrence rate is also examined.
3) Worsening rate of subjective symptoms
Proportion of patients who experienced worsening of subjective symptoms during the observation period of Nexium therapy
4) Peptic ulcer haemorrhage (yes/no)
Proportion of patients who experienced peptic ulcer haemorrhage during the observation period of Nexium therapy

10. Organisation to conduct the S-CEI

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

11. Contract partners of the operations to be outsourced, and scope of each contract

Contract partners:

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: Data management (data entry, CRF check/data fix, and dataset compilation)

12. Other required items

(1) Revision of the protocol
Following information is always examined 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 a 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 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 S-CEI if there is any of the 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.

Attachments

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)