Nexium Capsule

Protocol of Specific Clinical Experience Investigation for Long-term Use

(prevention of recurrence of gastric ulcer or duodenal ulcer with NSAIDs)

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 for prevention of recurrence of gastric ulcer or duodenal ulcer with non-steroidal anti-inflammatory drug (NSAID).

(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: 1000 (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 at least those enrolled to the phase III control study (studied in approx 130 patients for 52 weeks) in patients continuously given NSAIDs before approval.

In the long-term investigation of Omepral maintenance therapy for reflux oesophagitis, approximately 30 % of the enrolled patients were followed up for longer than one year. The target number of patients of this S-CEI is determined as 1000 to surely collect patients with one year of the administration period assuming that approximately 15 % of these patients are to be given Nexium for at least one year.

3. Patients to be enrolled

Patients who are given NSAIDs long terms to control pain due to a disease such as rheumatoid arthritis and osteoarthritis, and given Nexium for prevention of recurrence of gastric ulcer or duodenal ulcer for the first time.

(Patients who were previously given treatment with Nexium for gastric or duodenal ulcer can be enrolled.)

Exclusion criteria:

(1) Patients with gastric or duodenal ulcer in the baseline period (Endoscopic assessment by Sakita-Miwa classification: A1 or A2 (active stage) or H1 or H2 (healing stage)

(2) Patients who were previously given treatment with Nexium for prevention of recurrence of gastric or duodenal ulcer.

4. Observation period

One year

When treatment with Nexium or NSAID was completed/stopped within one year or patients stopped visiting the relevant physicians, the date and the reason are confirmed, and the period until the date is considered as the observation period.

5. Number of investigation sites where the investigation is conducted

Approx 200 sites majority of which is the orthopaedic surgery 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 heads 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, 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 treatment with Nexium. The physician enters his/her signature on the Form, and sends to “Nexium Capsule 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 within four weeks after the observation period is finished, and hands the CRF to the MR.

7. Investigation period

Registration period: Apr 2012 - Sep 2013

Investigation period: Apr 2012 - Sep 2014

8. Data to be collected

(1) Information required for patient identification

ID Number

(2) Patient demography data

age, sex, indication of NSAID (disease requiring pain control), history of peptic ulcer (disease name and the most recent onset period), in-patient/out-patient classification, height, weight, smoking history, drinking habits, Helicobacter pylori infection (yes/no), allergy (yes/no), CYP2C19 polymorphism (yes/no)

(3) The patient became pregnant during the observation period (yes/no) (if yes, expected delivery date)

(4) Past medical history and concurrent disease (other than indication of NSAID and peptic ulcer) yes/no (if yes, disease name)

(5) Previous treatment to prevent recurrence of peptic ulcer

drugs given within 4 weeks before Nexium (yes/no) (if yes, name of drug, administration route, daily dose (unit) and number of daily doses)

(6) Nexium administration

Nexium start date, unit dose, number of daily doses

When the initial dose was changed; changed unit dose and number of daily doses, date of the dose change, reason of the dose change

Status of drug compliance with Nexium

Whether Nexium was continued or stopped (if continued, the most recent administration date; if stopped, the last administration date and reason of discontinuation)

(7) Administration of NSAID

Name of NSAID, administration route, daily dose, start date

When NSAID was added/changed, the name of the second NSAID, administration route, daily dose, start date, reason of the addition/change

Drug compliance with the NSAID(s)

(8) Administration of concomitant drugs other than NSAID

Whether there were concomitant drugs during observation period of this S-CEI (yes/no) (if yes, name of drug, administration route, indication; in AE cases, daily dose (unit) and administration period)

(9) Concomitant therapy (other than medication)

Whether there was concomitant therapy during the observation period of this S-CEI (yes/no) (if yes, name of therapy, purpose of therapy; in AE cases, daily dose and period of the therapy)

(10) Clinical course

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, yes/no and severity* of individual symptoms e.g. epigastric pain, anorexia, bloating, heartburn, nausea, vomiting and belch)

* Severity is classified as below:

Mild (patients can endure signs and symptoms), Moderate (having discomfort which interrupts ADL), and Severe (activities of daily life (ADL) are interrupted)

(11) Adverse event

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

Serious adverse events: 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 gastric ulcer or duodenal ulcer and clinical symptoms in association with the recurrence (in “Endoscopic findings” and “Subjective symptoms” of “Clinical course” section in the 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 important medical event and 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

	at the time when Nexium is started	**Final observation day**, or at the time when Nexium is stopped***
Patient demography data	○	
Nexium administration	←	→
Administration of NSAID	←	→
Administration of concomitant drugs (other than NSAID)	←	→

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 final observation day is the most recent to the end of the observation period within 2 weeks before/after the end of the observation period. When the patient did not visit within 2 weeks before/after the end of the observation period, the final observation day is date of the last visit

*** The date when Nexium was stopped is the date of the last visit during the treatment or the next day of the date of the last administration of Nexium.

9. Data analysis: item and method

Definitions of the target population and the data analysis method 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, excluded patients and reason of the exclusion

(2) Patient demography

age, sex, BMI, in-patient/out-patient classification, smoking history, drinking habits, indication of NSAID, history of peptic ulcer, onset period (period between the most recent onset and start date of Nexium), allergy (yes/no), status of Helicobacter pylori infection, status of CYP2C19 polymorphism, past medical history, concurrent disease (liver disorder, renal disorder, Others)

(3) Treatment

Nexium unit dose, Nexium daily dose, previous treatment for prevention of recurrence of peptic ulcer (yes/no), major NSAID used to the patient, concomitant drug(s)* (yes/no and class of the drug(s)), concomitant therapy (yes/no)

*: including concomitant clopidogrel

(4) Safety

1) The numbers and frequencies of ADR/infection events sorted by SOC

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

3) The numbers and frequencies of serious adverse events sorted by SOC.

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

(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, on the non-recurrence rate is also examined.

3) Aggravation rate of subjective symptoms
Proportion of patients in whom aggravation of subjective symptoms was observed during treatment with Nexium