Nexium® Capsule
Protocol of Specific Clinical Experience Investigation
concerning *Helicobacter pylori* eradication

1. Objective

The objective of this investigation is to collect following data in patients given triple therapy for *Helicobacter pylori* eradication with Nexium + amoxicillin (AMPC) + clarithromycin (CAM), or Nexium + AMPC + metronidazole (MNZ) in usual post-marketing use.

(1) Efficacy (rate of *H. pylori* eradication)

(2) Development of ADRs

(3) Factors which may impact efficacy

(4) Factors which may impact safety

2. Target number of patients and its rationale

Target number of patients: 300
Rationale: When the eradication rate of the triple therapy is conservatively estimated as 80 %, about 250 subjects are required to estimate the rate of the accuracy 80 ± 5 % with two-tailed test (95 % Confidence Interval). The number is set as 300 considering patients to be withdrawn or excluded from the investigation. ADRs which may develop with the frequency of 1 % or higher are detected with a probability of 95 % or higher from 300 patients. Data of major events such as diarrhoea, loose stools, and dysgeusia can be collected from them.

3. Patients to be enrolled

Patients to whom triple therapy for *H.pylori* eradication to stomach is started after endoscopic treatment for gastric ulcer, duodenal ulcer, gastric MALT lymphoma, idiopathic thrombocytopenic purpura, or early gastric cancer as the approved indication of Nexium. Patients with *H.pylori* negative at the time when the triple therapy is started are excluded.

(1) The first line eradication: patients given Nexium + AMPC + CAM for *H.pylori* eradication for the first time (eradication-naive patients).

(2) The second line eradication: patients given Nexium + AMPC + MNZ after failure of previous eradication therapy with PPI (including Nexium) + AMPC + CAM

4. Observation period

Period from the start of triple therapy to assessment of eradication
Lengths of the observation periods are different among patients because the individual observation period is the period of the eradication therapy (7 days) + the period until assessment of eradication.

5. Number of investigation sites where the investigation is conducted

Approx 100 sites majority of which is the gastroenterological medicine department

6. Methods

(1) AZKK Medical Representatives (MRs) explain objectives, target patients and methods of this Specific Clinical Experience Investigation (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 before the S-CEI is started.

(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 the triple eradication therapy. The physician enters his/her signature on the Form, and sends to Nexium Capsule S-CEI Central Registration Centre by fax within 7 days after the triple eradication therapy 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

8. Data to be collected

(1) Information required for patient identification

ID Number

(2) Patient demography data

Age, sex, target disease, in-patient/out-patient classification, height, weight, smoking history, drinking habits, allergy (yes/no), CYP2C19 gene polymorphism status, sensitivity test to *H.pylori* antibacterial drugs (yes/no) (drug name and test result in case of “yes”) previous eradication therapy (period, drug names, unit doses, daily doses), Past medical history, Concurrent disease (yes/no) (if yes, disease name)

(3) Triple therapy

Triple therapy start date, unit dose of each drug, number of daily doses; When dosage was changed, unit dose of each drug after the change, number of daily doses, date of the dose change, reason of the change, discontinuation of triple therapy (yes/no) (if yes, the last administration date and reason of discontinuation)

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

(5) Concomitant drugs/drugs after the triple therapy until assessment of eradication

Concomitant drugs during the triple therapy, and drugs after the triple therapy until assessment of eradication (yes/no) (if yes, name of the drugs, administration route, indication, daily dose and administration period)

(6) Concomitant therapy (other than drugs)

Concomitant therapy during the triple therapy, and drugs after the triple therapy until assessment of eradication (yes/no) (if yes, name and purpose of the treatment; and the period of the therapy in patients who experience any adverse event)

(7) Diagnosis of *H. pylori* infection

Diagnosis of *H.pylori* infection: baseline and at the time of assessment of eradication after the triple therapy (date, method and result of diagnostic test)

(8) Adverse event

Terms and onset dates of all AEs* occurred during the observation period, outcome, date of outcome, seriousness**, causality with Nexium, factor other than Nexium, and lab test data relevant to the AE (test items, date and test data),
Information of serious adverse events includes 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)

*: In the case of development of fracture, community acquired pneumonia, enterocolitis in association with *Clostridium difficile* infection, information in detail including case narrative and data of relevant tests for diagnosis is collected as much as possible.

**: 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

(9) 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.

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, safety evaluable patients, 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, target disease, past medical history, concurrent disease (liver disorder, renal disorder, or others) allergy (yes/no), previous eradication therapy (yes/no)

(3) Treatment

Daily dose of triple therapy concomitant drug(s), concomitant drug(s) (yes/no), drug(s) after the triple therapy (yes/no), concomitant therapy (yes/no)

(4) Safety

1) Development of ADR/infections sorted by SOC

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

3) Development of ADR/infections is confirmed by patient demography and by treatment to discuss factors which may impact to safety.
Impact of concomitant drugs especially concomitant clopidogrel is to be confirmed.

(5) Development of serious adverse events sorted by SOC

(6) Development of the AEs of fracture, community acquired pneumonia, or enterocolitis in association with C*lostridium difficile* infection

(7) Efficacy

1) Eradication rate of triple therapy

2) Eradication rate by patient demography data and by treatment

3) Eradication rate is confirmed by patient demography and by treatment to discuss factors which may impact to efficacy.

4) Review of patient demography data and treatment in the patients who failed the eradication

10. 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 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 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.