**For Use in Application for Reexamination**

# Lyrica® Capsule

## Special Investigation

- Investigation on Long-term Use -

Protocol

Pfizer Japan Inc.

[redacted]

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[redacted]

**Introduction**

Pregabalin, an active ingredient of Lyrica Capsule (hereinafter called “the product”), is one of the derivatives of γ-aminobutyric acid (GABA) developed at Northwestern University, USA.
In the excessively stimulated excitable nervous system, pregabalin binds with high affinity to α2δ protein (an auxiliary subunit of voltage-gated calcium channels), which supposedly reduces calcium inflow into presynaptic nerve terminals and suppresses the synaptic release of excitatory neurotransmitters, consequently leading to manifestation of analgesic activity.
As of February 2012, the product has been approved for indications of neuropathic pain (peripheral neuropathic pain and central neuropathic pain) and the like in 120 countries of the world, including the US, European Union countries, Australia and Canada. In Japan, the product has been approved for indications of peripheral neuropathic pain in October 2010, pain associated with fibromyalgia in June 2012, and neuropathic pain in February 2013.

The special investigation on Lyrica Capsule (hereinafter called “the survey”) will be undertaken to collect or check information about the incidence of each type of disorder arising from adverse reactions to the product and the information on quality, efficacy and safety of the product in routine clinical use. The information collected through the survey will be supplied as the information on proper use of the product to medical facilities and used to prepare the application materials for reexamination of the product. To this end, the survey needs to be carried out in compliance with the Good Post-marketing Surveillance Practices (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 171, dated December 20, 2004). The case data collected through this survey will be reported to the MHLW pursuant to the Pharmaceutical and Medical Device Act. If applicable, the data including names of drugs, adverse reactions, gender and age by decade may be disclosed as a listing of patients in the “Pharmaceuticals and Medical Devices Safety Information” and “Pharmaceuticals and Medical Devices Information Website (http://www.info.pmda.go.jp)” which are issued and managed, respectively, by the MHLW. The collected case data may be also disclosed if the MHLW is requested to disclose them pursuant to the “Act on Access to Information Held by Administrative Organs” (Act No. 42, dated May 14, 1999). In any of the above cases, the report does not cover the name of the physicians, facilities or the like involved, and these pieces of information will never be published or disclosed.

## 1 Objectives

The objective of this survey is to evaluate the safety and efficacy of long-term use of the product in routine clinical practice. In addition, efforts will be made to collect information on the incidence of previously known and unknown adverse reactions that will occur under actual use conditions during the survey period. At the same time, the necessity of conducting a special investigation or a post-marketing clinical study will be evaluated.

The following events will be evaluated as major investigation items;

- Peripheral edema and edema-related events *
- Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury
- Vision-related events

*: Adverse events of the cardiovascular and respiratory systems will be also checked.

## 2 Study population

The survey covers the patients satisfying the following requirements:

- Patients who have been registered in the drug use investigation of the product, and are receiving continued administration as of 13 weeks after the start of administration of the product.

The indications, dosage and administration of the product are specified below:

| | |
|---|---|
| Indications: Neuropathic pain, pain associated with fibromyalgia* | |
| [Neuropathic pain] | |
| Dosage and Administration: | The usual starting dose in adults is 150 mg/day of pregabalin orally administered in 2 divided doses, which may be gradually increased to 300 mg/day over one week or longer. The dose may be adjusted depending on age and symptoms as appropriate, provided the daily dose may not exceed 600 mg and the product should be orally administered in 2 divided doses regardless of the daily dose.<br><br>The latest version of the package insert should be referred to when the product is prescribed. |

*: The survey does not cover pain associated with fibromyalgia.

## 3 Target sample size

The target sample size is 310 patients who have been treated for at least 52 weeks and for 104 weeks at most.

[Rationale]

Aiming at appropriate investigation of safety and efficacy of the product during long-term use, the target sample size was set at 310 patients, which is expected to have a 95% probability to detect adverse reactions occurring at the incidence of 1% (0.97%) or higher in at least one patient.

A total of 310 patients with neuropathic pain who have been examined in the observation period of at least 52 weeks will be recruited.

## 4 Planned survey period

The survey period and the period for registration into the survey are specified below:

Survey period* : April 2011 to April 2017

Registration period** : April 2011 to August 2016

* A contract will be concluded on or after the first day of the survey period, and registration of patients will be subsequently started. Observation of all registered patients will be

completed by the last day of the contract period. An exception is when a contract for the present investigation is newly concluded with a study site where only the drug use investigation of the product was conducted.

** Patients will be confined to those who have been registered in the drug use investigation of the product by September 2015.

## 5 Survey procedures

5.1 Survey method

In this survey, all patients who satisfy the eligibility criteria for the survey at the study site after conclusion of the contract will be registered. However, when a contract for the present investigation is newly concluded with a study site where only the drug use investigation of the product was conducted, all patients who have been registered in the drug use investigation of the product in March 2013 or earlier and satisfy the eligibility criteria for this survey will be registered, even if patients' participation in the drug use investigation was before conclusion of the contract for this survey.

5.2 Data collection method

During this survey, an Internet-based electronic data collection system for post-marketing surveillance will be used for patient registration, survey data entry and data confirmation. PPD of (hereinafter called "the system") will be utilized for this survey. Security during data transmission will be ensured by authenticating each investigator with individual user ID and password and using the latest protocol for SSL enciphered communication. Detailed procedure and methods for data entry, correction and confirmation are separately specified in the data entry sample, etc.

5.3 Patient registration

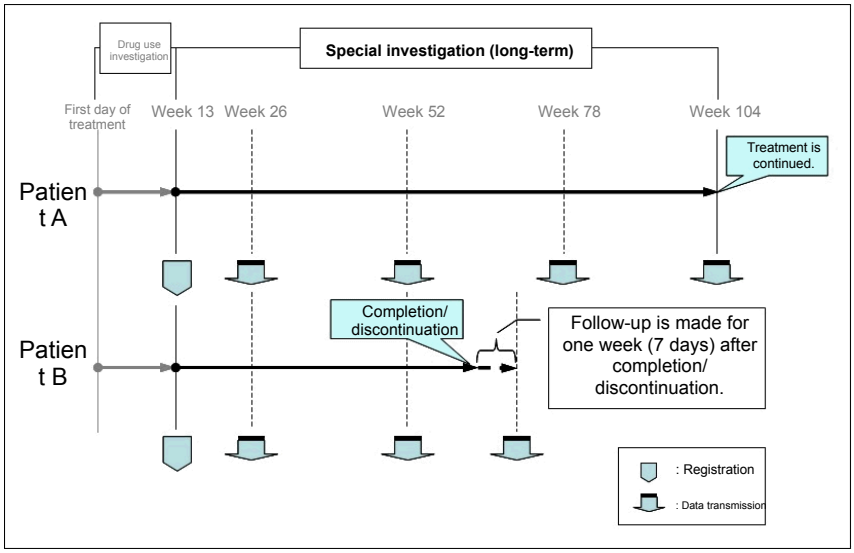
After the user ID and password are issued to each investigator, the investigator will enter the following basic information on the patient registration screen: name initials of the patient (as needed), ID code, gender, birth date, starting date for treatment with the product and eligibility to the survey.

5.4 Observation period

The observation period of this survey will occur in succession to the 13-week observation period of the drug use investigation. It will start from Week 14 and last until Week 104 (Day 728 from the start of treatment counted as Day 1). However, in cases where treatment has been completed or discontinued before Week 104, observation will continued until completion (discontinuation) of treatment, and follow-up will be made for one week (7 days) after completion (discontinuation) of treatment. Completion of treatment means cases where further treatment with the product is judged unnecessary because of achievement of the purpose of treatment set at the start of treatment (e.g., cure of target diseases).

During this survey, safety will be evaluated on the day of the first visit after Week 26, Week 52, Week 78, and Week 104 (including the last day of each observation period), as a rule. In cases where treatment has been completed or discontinued, safety will be evaluated until the day of the first visit following 7-day period after the completion (discontinuation) of treatment, and safety information will be collected for this period.

The investigator will complete and send the survey forms at Week 26, Week 52, Week 78, and Week 104.




Supplementary note: Completion of treatment means cases where further treatment with the product is judged unnecessary because of achievement of the purpose of treatment set at the start of treatment (e.g., cure of target diseases).

5.5 Precautions in data entry, correction and confirmation

(1) Data entry

The investigator should check each survey item and enter and transmit the data into the system, on the basis of the records of healthcare (medical records, test reports, etc.). Data entry sample, etc. should be referred to for detailed procedure.

(2) Data correction

If Pfizer Japan Inc. (hereinafter called “the sponsor”) places inquiry about the entered information, the investigator should check the above-mentioned healthcare records again and, as needed, correct the once entered data and transmit the corrected data. Data entry sample, etc. should be referred to for detailed procedure.

(3) Data confirmation

Upon completion of entry and correction of all survey data, the investigator should check the survey form and attach his/her electronic signature to it. Data entry sample etc. should be referred to for detailed procedure.

5.6 Use of information from drug use investigation

In this survey, information from the “Drug Use Investigation of Lyrica Capsule” will be used as the information for background variables and the first 13 weeks of administration.

## 6 Items and schedule of survey

The investigator will conduct the survey in accordance with the observation schedule given below. After conclusion of the contract on the survey, the investigator will register eligible patients. Then, the investigator will check the data on each registered patient (including the data on background variables at the start of treatment) and fill in the survey form for each patient.

Observation schedule

| Survey items \ Time | | Registration form: At registration *1 | Survey form Volume 1: Observation period: Week 26 | Survey form Volume 1: Observation period: Week 52 | Survey form Volume 2: Observation period: Week 78 | Survey form Volume 2: Observation period: Week 104 (or completion/ discontinuation)*2 | Each volume*2: Observation period: 7 days after completion/ discontinuation |
|---|---|---|---|---|---|---|---|
| Identifiable patient information | ID code | ○ | | | | | |
| | Name initials (not indispensable) | ○ | | | | | |
| | Gender | ○ | | | | | |
| | Birth date | ○ | | | | | |
| Eligibility | | ● | | | | | |
| Pregnancy status (females only) | | | ● | ● | ● | ● | |
| Records of treatment with the product | | | ← | — | — | — | → |
| Concomitant therapy (drug therapy/non-drug therapy) | | | ← | — | — | — | → |
| Tests (clinical findings/laboratory test) | | | ← | — | — | — | → |
| (1) Body weight | | | ● | ● | ● | ● | |
| (2) Clinical findings | 1. [Presence/absence of peripheral edema or edema in general], [Presence/absence of dizziness, somnolence, loss of consciousness, syncope or potential for accidental injury], [Presence/absence of ophthalmological abnormalities], [Presence/absence of suicidal ideation (including suicide attempt and suicide after start of treatment)], [Presence/absence of pathologic changes in appetite and activity] | | | | | ● | |
| | 2. [Presence/absence of withdrawal symptom/rebound phenomenon] | | | | | | ● |
| (3) Presence/absence of hyperalgesia | | | | | | ● | |
| (4) Laboratory test | | | ← | — | — | — | → |
| Clinical evaluation | (1) Patient-rated pain score (2) Patient-rated sleep disorder score | | ● | ● | ● | ● | |
| | (3) Patient's impression (PGIC) (4) Physician's impression (CGIC) | | ● | ● | ● | ● | |
| Patient summary | | | ● | ● | ● | ● | |
| Efficacy evaluation | | | | | | ● | |
| Adverse events | | | ← | — | — | — | → |

● Data to be entered; ○ Data to be reflected

1): Entry at the time of patient registration. Information from the drug use investigation will be used except for "eligibility."

2): In cases where treatment has been completed (discontinued) before the end of the observation period, follow-up is made for one week (7 days) after completion (discontinuation) of treatment.

## 6.1 Background variables

(1) The information at the start of this survey will be entered in the patient registration form.

[1] Eligibility

(2) In the same manner as in the 13-week observation period of the drug use investigation, the following information up to the day of safety evaluation at each time point of observation will be entered.

[1] Pregnancy status and date of delivery/planned date of delivery (females only)

6.2 Records of treatment with the product

In the same manner as in the 13-week observation period of the drug use investigation, the following information about the product use up to the day of safety evaluation at each time point of observation will be entered.

[1] Daily dose
[2] Number of doses per day
[3] Dosing regimen (morning/noon/evening/bedtime, before meal/after meal/others)
[4] Dosing period

In cases receiving hemodialysis, the following information will be also entered:

[5] Frequency of dialysis
[6] Duration of each session of dialysis
[7] Supplemental dose after dialysis

6.3 Concomitant therapy

(1) Drug therapy

In the same manner as in the 13-week observation period of the drug use investigation, the following information will be entered about all drugs administered by the day of safety evaluation at each time point of observation. If any adverse event occurs, information will be also entered about the concomitant drugs used during the period from the first day of treatment to the onset of the adverse event. Medications used for the treatment of the adverse event should be also recorded.

[1] Name of drug (brand name)
[2] Route of administration
[3] Daily dose
[4] Number of doses per day
[5] Dosing period
[6] Reasons for the use of drugs

(2) Non-drug therapy

In the same manner as in the 13-week observation period of the drug use investigation, the following information will be entered about the non-drug therapies used by the day of safety evaluation at each time point of observation. If any adverse event occurs, information will be also entered about the non-drug therapies used during the period from the first day of treatment to the onset of the adverse event. The non-drug therapies used for the treatment of the adverse event should be also recorded.

[1] Name of therapy
[2] Period of use
[3] Reason for use

6.4 Tests (clinical findings/laboratory test)

(1) Body weight

In the same manner as in the 13-week observation period of the drug use investigation, the following information obtained at Week 26, Week 52, Week 78, and Week 104 and by the day of safety evaluation at each time point of observation will be entered. If the investigator

considers that the change in body weight from the pre-treatment level is abnormal, it will be reported as an adverse event.

[1] Date of evaluation
[2] Results

(2) Clinical findings

In the same manner as in the 13-week observation period of the drug use investigation, the following information up to the day of safety evaluation at the time point of last observation will be entered. In cases where treatment has been completed or discontinued before Week 104, the data at the time of completion (discontinuation) of treatment will be entered. If the investigator considers that the change in any of the clinical findings from the pre-treatment status is abnormal, it will be reported as an adverse event.

(2)-1 Information after the 13-week observation period of the drug use investigation and up to the day of safety evaluation at the time point of last observation

[Presence/absence of peripheral edema or edema in general][*], [Presence/absence of dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury], [Presence/absence of ophthalmological abnormalities], [Presence/absence of suicidal ideation (including suicide attempt and suicide after start of treatment)], [Presence/absence of pathologic changes in appetite and activity]

| |
|---|
| Supplementary note[*]: In cases where peripheral edema or edema in general is found, adverse events of the cardiovascular and respiratory systems also need to be checked. If any clinically significant change from the pre-treatment condition is found, it should be entered in detail in the field for adverse events. |

(2)-2 Information in cases of completed (discontinued) treatment with the product (information on the day of safety evaluation following 7-day period after the day of discontinuation [including Day 7 of this period])

[Presence/absence of withdrawal symptom/rebound phenomenon]

(3) Presence/absence of hyperalgesia

Information will be entered about the presence/absence of hyperalgesia at Week 104. In cases where treatment has been completed or discontinued before Week 104, the data at the time of completion (discontinuation) of treatment will be entered. If the investigator considers that the change in the condition of hyperalgesia from the pre-treatment status is abnormal, it will be reported as an adverse event.

(4) Laboratory test

In the same manner as in the 13-week observation period of the drug use investigation, the data on the following laboratory parameters tested by the day of safety evaluation at each time point of observation will be entered. If the investigator considers that the change in any of the following parameters from the pre-treatment level is abnormal, it will be reported as an adverse event.

(Serum creatinine, serum amylase, serum total thyroxine [T4], thyroid stimulating hormone [TSH], blood glucose [fasting level], hemoglobin A1c [HbA1c])

[1] Date of measurement
[2] Results

6.5 Clinical evaluation

(1) Patient-rated pain score

At Week 26, Week 52, Week 78, and Week 104, the pain experienced during the past 24 hours will be rated at the time of getting up in the morning on a 11-grade scale, ranging from 0 (no pain) to 10 (the most severe pain possible). In cases where treatment has been completed or discontinued before Week 104, the data at the time of completion (discontinuation) of treatment will be entered.

(2) Patient-rated sleep disorder score

At Week 26, Week 52, Week 78, and Week 104, the sleep disorder (inability to sleep because of pain) experienced during the past 24 hours will be rated at the time of getting up in the morning on a 11-grade scale, ranging from 0 (no disturbance of sleep) to 10 (totally unable to sleep because of pain). In cases where treatment has been completed or discontinued before Week 104, the data at the time of completion (discontinuation) of treatment will be entered.

(3) Patient's impression (Patient Global Impression of Change [PGIC])

The patient's impression about the condition at Week 26, Week 52, Week 78, and Week 104, as compared to the condition before the start of treatment (including the first day of treatment), will be rated on a 7-grade scale, ranging from 1 (markedly improved) to 7 (markedly worsened). In cases where treatment has been completed or discontinued before Week 104, the data at the time of completion (discontinuation) of treatment will be entered.

1. Markedly improved 2. Improved 3. Slightly improved 4. Unchanged
5. Slightly worsened 6. Worsened 7. Markedly worsened

(4) Physician's impression (Clinical Global Impression of Change [CGIC])

The physician's impression about the condition at Week 26, Week 52, Week 78, and Week 104, as compared to the condition before the start of treatment (including the first day of treatment), will be rated on a 7-grade scale, ranging from 1 (markedly improved) to 7 (markedly worsened). In cases where treatment has been completed or discontinued before Week 104, the data at the time of completion (discontinuation) of treatment will be entered.

1. Markedly improved 2. Improved 3. Slightly improved 4. Unchanged
5. Slightly worsened 6. Worsened 7. Markedly worsened

If administration of the product is continued in spite that the condition has been rated as 4 to 7 on CGIC, one reason for continuation should be selected from the followings.

- Patient's request
- Alternative treatment is difficult.
- Drug assessment is halfway.
- Others

6.6 Patient summary

The appropriateness of continuation of treatment with the product will be checked on the day of safety evaluation at each time point of observation. In cases where continuation of treatment with the product is not possible, one major reason should be selected from the alternatives given below. If adverse events, abnormalities in laboratory parameters or the death of patient is selected as a major reason, the relevant data should be entered in the "adverse event" field.

[1] Insufficient clinical efficacy
[2] Recovery (effective)
[3] Adverse events
[4] Abnormalities in laboratory parameters
[5] Death of patient
[6] Lost to follow-up
[7] Others

In cases where no revisit has been made after the day of safety evaluation in the drug use investigation, it should be entered in the "Confirmation of revisit after the day of safety

evaluation in the drug use investigation" field.

6.7 Efficacy evaluation

The efficacy of the product at Week 104 as compared to the condition before the start of treatment (including the first day of treatment) will be evaluated in the following way, and the judgment will be entered. In cases where treatment has been completed or discontinued before Week 104, the data at the time of completion (discontinuation) of treatment will be entered.

[1] Date of efficacy evaluation

[2] Clinical efficacy

- Effective
- Ineffective
- Impossible to judge (enter the reason)

Items of evaluation

The reason for judging "effective" or "ineffective" should be entered (multiple choices allowed).

- Changes in clinical symptoms
- Others

6.8 Adverse events

For evaluation of safety, the incidence of adverse events following the start of treatment with the product will be checked, and the following information will be entered. If any adverse event occurs, the investigator should take appropriate measures and immediately report it to the sponsor. When the causal relationship between the event and the product cannot be ruled out, observe the course of event or its sequela until they disappear or become stabilized at the level acceptable for the investigator and the sponsor.

A detailed investigation will be separately carried out if patients have intrauterine exposure or develop serious adverse reactions, adverse reactions not listed in the package insert and the like occur and the sponsor deems it necessary.

[1] Day of safety evaluation (as a rule, day of last visit within 29 days after the start of treatment)
[2] Presence/absence of adverse events
[3] Name of adverse event
[4] Date of onset
[5] Measures taken
[6] Seriousness
[7] Outcome
[8] Causal relationship to the product

[The following information should be entered if the adverse event is associated with abnormal changes in test data such as laboratory tests.]

[1] Name of test
[2] Reference value at the facility
[3] Unit
[4] Date of measurement
[5] Results

Supplementary note: Adverse events mean all events unfavorable for the patient, arising after the start of treatment with the product, regardless of presence/absence of causal relationship to the product (including clinically significant abnormal changes in laboratory parameters). Serious adverse events mean death, life-threatening events, and events possibly causing hospitalization, extension of hospital stay period, permanent or marked disorders/disabilities, congenital anomalies/defects or other medically significant events/disorders.

6.9 Major investigation items

The following events should be evaluated as major investigation items in this survey.

[1] Peripheral edema and edema-related events

Information will be collected about the presence/absence of events related to peripheral edema and the course of patients before and after the onset of events. The situations on development of these events will be analyzed by means of factor analysis, including analysis of the site affected, dose of the product, concomitant therapy, background variables, etc. The package insert gives precautions on congestive heart failure in patients presenting symptoms related to edema. In 30 overseas placebo-controlled studies, the incidence of hypertension and dyspnea was higher in the patients developing peripheral edema than in patients free of peripheral edema, although the incidence of the other events did not differ markedly between these two groups. In view of these facts, information on cardiac function and the incidence of adverse events of the respiratory system will be also collected.

[2] Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury

Information will be collected about the presence/absence of events related to dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury and the course of patient's condition before and after the onset of events. The situations on development of these events will be analyzed by factor analysis, including analysis of the dose of the product, concomitant therapy, background variables and so on.

[3] Vision-related events

Information will be collected about the presence/absence of events related to the eyes and the course of patient's condition before and after the onset of events. The situations on development of the events will be analyzed by factor analysis, including analysis of the dose of the product, concomitant therapy, background variables and so on.

Patients developing adverse events included in the major investigation items will be separately investigated in detail if the sponsor deems it necessary.

## 7 Analysis plan

7.1 Analysis set

As a rule, safety analysis set will include patients who satisfy the eligibility criteria and have been confirmed to have taken the product at least once. As a rule, efficacy analysis set will include patients who are evaluable for efficacy in accordance with the separately set analysis plan (i.e., patients in whom efficacy was considered to be appropriately evaluated).

7.2 Methods of analysis

7.2.1 Safety analysis

In the safety analysis set, the status of onset of adverse reactions and incidence of adverse reactions (percentage of patients developing adverse events for which the causal relationship with the product cannot be ruled out) will be set as primary analysis items. The factors affecting the incidence of adverse reactions will be also analyzed, for example, the incidence of adverse events will be summarized for each of the factors including background variable.

7.2.2 Efficacy analysis

In the efficacy analysis set, the response rate will be set as a primary analysis item. As needed, explorative analysis of factors affecting the efficacy will be also carried out.

7.3 Time of analysis

7.3.1 Periodical safety report

Interim analysis will be conducted at intervals of 6 months during the first two years after approval of the product and once a year during the subsequent reexamination period.

7.3.2 Submission of application for reexamination

Final analysis will be conducted upon completion of the reexamination period.

## 8 Publication of the results

Pfizer Japan Inc. will publish the results of one of the following surveys. As needed, the company will publish the results of survey at academic society meetings, in journals and so on for the purpose of supplying information for proper use of the product.

- The survey registered in www.clinicaltrials.gov (ClinicalTrials.gov), regardless of the reason for registration
- Other survey judged to have yielded scientifically or medically significant results

The timing for publication of the survey results will be determined based on whether or not the product has been approved in any country at the completion of the survey on the product.

The results of the survey on the product already approved in a given country should be published within one year after fixation of the patient's data collected during the last visit.

Only the published papers which can be accessed via the widely accepted and searchable databases on papers will be cited.


## 10 References

Attachment 1: Adverse event report