Anaemetro I.V. Infusion 500 mg Drug Use Investigation

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

[redacted]

[redacted]

STUDY INFORMATION

Title	Anaemetro I.V. Infusion 500 mg Drug Use Investigation
Protocol number	A6831007
Protocol version identifier	Amended1
Date of last version of protocol	01 April 2015
Active substance	Metronidazole
Medicinal product	Anaemetro I.V. Infusion 500 mg
Research question and objectives	This study will be conducted to investigate the safety and effectiveness of Anaemetro I.V. Infusion 500 mg in daily clinical practice. Additionally, it is intended to assess the following: • Adverse reactions unexpected from precautions, and • Occurrence of adverse reactions under actual clinical settings "Central nervous system disorder" also will be confirmed for the tendency of adverse reactions under actual clinical settings.
Author	PPD Post Marketing Study Strategy and Management PMS Planning & Operation Group 1

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Acronym	Tittle
AE	*adverse event*
CRF	*case report form*
CRP	*C-reactive protein*
EDP	*exposure during pregnancy*
ID	*identification*
IEC	*independent ethics committee*
IRB	*institutional review board*
MHLW	*Ministry of Health, Labour and Welfare*
MIC	*minimum inhibitory concentration*
N/A	*not applicable*
NIS	*non-interventional study*
PID	*pelvic inflammatory disease and other related diseases*
PMDA	*Pharmaceuticals and Medical Devices Agency*
RMP	*Risk Management Plan*
SAE	*serious adverse event*
SAP	*statistical analysis plan*
SRSD	*Single Reference Safety Document*
WBC	*white blood cell*

2. RESPONSIBLE PARTIES

The Japan Good Post marketing Study Practice officer

Principal Investigator(s) of the Protocol

N/A

3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
Amended1	10 January 2017	Other amendment(s)	4. 7.2.4.	Section 4. Change in the end of data collection from "March 2017" to "May 2017" Section 7.2.4. Change in investigation period from "April 2015 to March 2017" to "April 2015 to May 2017" and change in registration period from "April 2015 to January 2017" to "April 2015 to March 2017"	It was decided to extend investigation period and registration period another 2 months, since it is possible that the target number of patients in the safety analysis set would not be reached by the end of the registration period planned in this study.

4. MILESTONES

Milestone	Planned date
Start of data collection	April 2015
End of data collection	May 2017
Final study report	To be decided

5. RATIONALE AND BACKGROUND

Anaemetro I.V. Infusion 500 mg (hereinafter referred to as "this drug") is an injection of metronidazole, which has been used for a long time in Japan. Metronidazole has a strong antibacterial or antiprotozoan activity against obligate anaerobes or protozoa respectively; for which, it is recommended in various domestic and overseas guidelines and textbooks, and highly regarded as a therapeutic method for anaerobic infection.

Anaerobic infection developed in patients with severe underlying diseases frequently becomes more refractory or serious due to the patients' susceptibility to infection. Patients in such a serious condition often have difficulties taking oral medications, and thus, metronidazole injection would be beneficial.

Such background warrants the great clinical significance to make metronidazole injection clinically available; for which, Pfizer obtained the approval to manufacture and market this drug in Japan in July 2014.

The drug use investigation of Anaemetro I.V. Infusion 500 mg (hereinafter referred to as "this study") shall be conducted to collect information regarding the occurrence by type of adverse reactions associated with this drug in daily clinical practice, and information regarding the quality, effectiveness, and safety of this drug. The information collected from this study shall be used to provide proper use information and prepare documents for the application of re-examination.

This study shall be conducted in strict compliance with the "MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171 dated December 20, 2004).

Data obtained from the patients registered in this study will be reported to the MHLW pursuant to the Pharmaceutical and Medical Device Act; pertinent to which, data may be publicly posted in MHLW's "Pharmaceuticals and Medical Devices Safety Information" and "Pharmaceuticals and Medical Devices Information Website (http://www.info.pmda.go.jp) as a listing of patients, which will present the names of drugs, adverse reactions, sex, age (increment of 10 years), and other relevant information. Furthermore, data collected may also be disclosed if the MHLW is required to disclose such information in accordance with the "Act on Access to Information Held by Administrative Organs" (Law No. 42 dated May 14, 1999) provided that in no event will the names of physicians, medical institutions, and other personal information be subject to such disclosure, nor will it be posted or disclosed in any form or shape.

6. RESEARCH QUESTION AND OBJECTIVES

This study will be conducted to investigate the safety and effectiveness of this drug in daily clinical practice. Additionally, it is intended to assess the following:

- Adverse reactions unexpected from precautions, and
- Occurrence of adverse reactions under actual clinical settings

"Central nervous system disorder" also will be confirmed for the tendency of adverse reactions under actual clinical settings.

6.1. Safety specifications

[Important Identified Risks] Central nervous system disorder

7. RESEARCH METHODS

7.1. Study design

This study is a multicenter open-label study conducted in patients receiving this drug; for which, case report forms (CRFs) will be recorded based on data presented in medical records obtained in daily clinical practice.

7.2. Setting

Patients who satisfy all of the inclusion criteria are subject to this study.

7.2.1. Inclusion criteria

Patients who have not used metronidazole (injection) in the past, and have been administered this drug for treatment of anaerobic infection, infectious enterocolitis, or amebic dysentery. Patients who have used metronidazole (oral agent and vaginal tablet) in the past are eligible, and should not be excluded from this study.

7.2.2. Exclusion criteria

No exclusion criteria are set out in this study.

7.2.3. Sites for this study

The sites with presence of doctors specialized in the target therapeutic area primarily in the following departments, at which, this drug can be prescribed:
Gastroenterology, gastroenterological surgery, respiratory medicine, gynecology, and infection

7.2.4. Planned investigation period

Investigation period: April 2015 to May 2017
Registration period: April 2015 to March 2017
(Even before the end of the registration period, registration will be discontinued if the target number of patients is reached)

7.2.5. Study methods

This study will be a prospective study, in which, patients will be registered with central registration system until the target number of patients meeting the registration criteria are reached.

7.2.6. Observation period

The observation period shall start on the day the treatment with this drug begins and end on the day the treatment is completed; however, it shall be cut off at Week 8 after the initiation of treatment (Day 56 counting from Day 1 as the day the treatment begins) if the treatment is prolonged.

7.3. Variables

This study will be conducted in accordance with the following variables/schedule of observation (Table 1).

Table 1. Variables/schedule of observation

Variables \ Timing		Initiation of treatment	Observation period	Completion of observation period
Background	ID number	●		
	Sex	●		
	Age (on the date of treatment initiation)	●		
	Height/body weight	●		
	Hospitalization status (inpatient/outpatient)	●		
	Targeted disease	●		
	Medical history	●		
Targeted drug use record		●		
Concomitant therapy (Drug therapy)		●		
Vital sign/laboratory tests (body temperature, WBC count, and CRP)		●		
Microbiological test		●		
Effectiveness evaluation				●
End-of-study (discontinuation) record				●
Adverse events		●		

●: Data items to complete

7.3.1. Background

Input the information at the initiation of treatment with this drug.

[1] ID number

[2] Sex

[3] Age

[4] Height

[5] Body weight

[6] Hospitalization status (inpatient/outpatient)

[7] Targeted disease (infection for which this drug is used)

- Name of disease
- Severity

[8] Medical history (information except for targeted disease)

- Presence/absence of hepatic functional impairment or renal functional impairment

- Name of disease or syndrome other than the above, as well as the history or the complication

[9] History of surgery if the targeted disease is a secondary infection due to surgery

- Disease name for which the surgical operation is performed
- Date of surgery

7.3.2. Targeted drug use record

The following will be recorded for the targeted drug.

[1] Daily dose

[2] Number of doses per day

[3] Treatment period (start date/end date)

[4] Reason for change of dose

7.3.3. Concomitant therapy

7.3.3.1. Drug therapy

Medications used for the infection

The following information will be recorded for medications used for the infection during a period from 14 days before the initiation of treatment with this drug to the completion date of observation period.

[1] Drug name (product name)

[2] Route of administration

[3] Date of treatment initiation

[4] Presence/absence of concomitant use at the time the treatment with this drug begins

7.3.4. Tests

7.3.4.1. Vital sign/laboratory tests

Vital sign/laboratory tests

Record the following vital sign/laboratory parameters before the initiation of treatment with this drug, during the observation period, and at the completion of observation period.

[Vital sign/laboratory parameters] Body temperature, WBC count, and CRP

- Test date

- Test results

7.3.4.2. Other tests

Microbiological test

Record the pathogen for which this drug is used, and the expected results of test on the causative organism. Record the following information before the initiation of treatment with this drug, during the observation period, and at the completion of observation period.

[1] Specimen

[2] Pathogen, and the name of causative bacterial strain

[3] Date of sampling

[4] Test method

[5] Pathogen result (Semi-quantitative) (-, +, ++, +++, Unknown)

[6] MIC of this drug

[7] Presence/absence of ameba protozoa

7.3.5. End-of-study (discontinuation) record

If the observation is completed or discontinued before the end of the longest observation period (8 weeks), the reason should be recorded.

If an adverse event (AE) is selected for the reason, the information in details should be recorded in the AE column.

[Reason for completion]

- Cured (effective)

[Reason for discontinuation]

- Insufficient clinical response
- AE
- Hospital transfer
- Others

Presence/absence of pregnancy on the completion date of the observation period (if present, the delivery date or expected date of delivery)

7.3.6. Effectiveness evaluation

(1) Clinical response

The clinical response of this drug should be evaluated comprehensively at the completion of the observation period, and the results should be recorded.

If this drug is administered continuously for more than 8 weeks, the clinical response should be evaluated comprehensively at Week 8.

- Effective
- Not effective
- Indeterminate (the reason should be recorded.)

The assessment criteria shall be as follows:

Table 2. Assessment criteria for [anaerobic infection] / [infectious enterocolitis (including pseudomembranous colitis)]

Assessment	Definition
Effective	Clinical symptoms accompanying the infection observed at the initiation of treatment with this drug has improved at the time of assessment, and treatment with other antibacterial drugs after the time of assessment is determined not necessary.
Not effective	"Effective" criteria are not met.
Indeterminate	Clinical response is difficult to evaluate.

Table 3. Assessment criteria for [amebic dysentery]

Assessment	Definition
Effective	Clinical symptoms accompanying the infection observed at the initiation of treatment with this drug has improved at the time of assessment, and treatment with other antibacterial drugs other than antiamebic agents (paromomycin, etc.) after the time of assessment is determined not necessary.
Not effective	"Effective" criteria are not met.
Indeterminate	Clinical response is difficult to evaluate.

Any clinically problematic finding compared to the initiation of treatment should be recorded in details in the AE column.

(2) Rationale for clinical response assessment

The rationale for the clinical response assessment ("Effective" or "Not effective"), on the disease for which this drug is used, should be recorded.

[Anaerobic infection]

General clinical findings, body temperature, WBC count, CRP level, imaging, and others

[Infectious enterocolitis (including pseudomembranous colitis)]

General clinical findings, Clostridium difficile TOXIN test, frequency of diarrhea, body temperature, abdominal pain, and others

[Amebic dysentery]

General clinical findings, ameba test, frequency of diarrhea, body temperature, abdominal pain, and others

(3) Microbiological response assessment

Microbiological response at the completion of observation period compared to prior to the initiation of treatment with this drug should be assessed, and the results should be recorded.

Table 4. Assessment criteria for microbiological response

Assessment	Definition
Eradication	Pathogen is not detected in the specimen appropriately collected following administration of this drug.
Presumed eradication	Pathogen is presumed eradicated if the treatment improves or resolves the clinical symptoms, and a specimen suitable for the test is no longer available in the original infection focus.
Partial eradication	Pathogen is partially detected in the specimen appropriately collected following administration of this drug.
Persistence	No improvement of clinical symptoms is confirmed, and the pathogen is detected in the infection focus.
Indeterminate	A microbiological test was conducted, but no pathogen could be isolated or estimated. Or a microbiological test was not conducted due to various reasons.

7.3.7. Adverse events

After confirming the occurrence of AEs from the initiation of treatment with this drug to the completion date of observation period, the following information will be recorded. Upon occurrence of any AE, the investigator should take appropriate measures, and promptly report to Pfizer Japan Inc. (hereinafter "Sponsor"), and if causal relationship with this drug cannot be ruled out, the investigator should follow up the event until the AE or its sequelae are resolved or stabilized at the level acceptable to the investigator and Sponsor.

Moreover, a study should be separately conducted in detail on patients in whom a serious adverse reaction, or an adverse reaction not described in the package insert occurred if it is determined necessary by Sponsor.

[1] Presence/absence of AE

[2] Name of AE

[3] Presence/absence of AE concerning central nervous system disorder

[4] Date of occurrence

[5] Intervention

[6] Seriousness

[7] Outcome

[8] Causal relationship

[If the AE is associated with abnormal change in laboratory values, i.e., clinical laboratory tests, the following information should also be recorded.]

[1] Laboratory parameter

[2] Site reference value

[3] Unit

[4] Date measured

[5] Results

Detailed study on adverse reactions concerning central nervous system disorder

Completion of detailed CRF should be separately requested on central nervous system disorder that occurred in patients subject to this study if it is determined necessary by Sponsor.

7.3.8. Major investigation items

N/A

7.4. Data sources

In this study, the investigator extracts the necessary information from the medical record in accordance with the protocol.

7.5. Study size

7.5.1. Planned sample size

100 patients (for safety analysis)

7.5.2. Rationale for sample size

The target sample size was set to be 100 patients, which should enable to detect, at 95% probability, an adverse reaction of which the true incidence rate is 3% in reference to adverse reaction of the least incidence in a clinical study of this drug (Study A6831005). This sample size should enable to confirm whether the types and incidence of adverse reaction related to this

drug used for diseases other than intra-abdominal infection, and pelvic inflammatory disease and other related diseases (hereinafter referred to as "PID") that were targeted in the clinical study would be similar to those occurred in Study A6831005.

Events specified as important identified risks or important potential risks in the Risk Management Plan (RMP) may not have a high incidence, and thus, may not detect sufficient information only from the drug use investigation; nonetheless, such an event collected in the drug use investigation should be investigated within the framework of the drug use investigation. Moreover, these events should also be monitored through the routine pharmacovigilance activities.

The sample size of 100 patients are expected to enable accumulating data on the number of patients at the level similar to the clinical study in terms of clinical response rate of this drug for diseases other than intra-abdominal infection and PID that were targeted in the clinical study and also in terms of clinical response rate in subgroup analysis by each major indication; which should enable verification whether the effectiveness under actual clinical settings is similar to the results of the clinical study.

7.6. Data management

7.6.1. Data collection method

The data for this study will be collected using a specific CRF provided by Sponsor. The investigator will complete the CRFs promptly after the completion of observation period and submit them to the Sponsor.

7.6.2. Patient registration

7.6.2.1. Procedure of patient registration

(1) Registration

The following registration items should be completed in the registration forms for patients with anaerobic infection, infectious enterocolitis, or amebic dysentery who are given Anaemetro I.V. Infusion 500 mg and meet the registration requirements; patients should be registered via FAX at the registration center until the target number of patients is registered. The patients should be registered before Day 8 of treatment counting from the initiation of treatment with Anaemetro I.V. Infusion 500 mg as Day 1.

1) Registration criteria

Patients who have not used Anaemetro I.V. Infusion 500 mg before the initiation of treatment with this drug

2) Registration items

Patient ID number, sex, age on the date of treatment initiation, date of treatment initiation with this drug, eligibility to registration criteria, and disease targeted in this study (disease for which this drug is used)

[Patient Registration Center]

FAX: 0120–771–297 (Available 24 hours a day)

(2) Exclusion from the registration

Patients found to not meet the registration criteria after the registration form is received at the registration center will be excluded from the registration.

7.6.3. Reminders concerning completion, revision, and submission of case report form

7.6.3.1. Completion

The investigator shall, upon confirming the study items, complete the CRF based on medical charts and other medical records such as relevant test results, using a pen, ballpoint pen, or other inerasable means.

7.6.3.2. Revision

Upon receiving Sponsor's inquiry on the contents of the CRF (query forms), the investigator will again confirm the contents of medical records described earlier, and as required, correct relevant sections and resubmit the form. Corrections in the CRF should be struck out with a double line (=) with a "correction seal" on the double line; the double line should be drawn so that the original contents prior to correction are legible.

7.6.3.3. Submission

CRFs should be submitted promptly upon completion in accordance with the procedures set out by Sponsor.

7.7. Data analysis

The details of methods of analysis on data collected in this study shall be described in the statistical analysis plan (SAP) to be separately prepared.

・ Definition of analysis set

The safety analysis set shall include patients for whom the registration in this study and administration of this drug have been confirmed.

Two analysis sets, which are clinically-evaluable analysis set and microbiological analysis set shall be defined as the effectiveness analysis set. The clinically-evaluable analysis set includes patients who were confirmed to conduct the clinical evaluation in the safety analysis set. The microbiological analysis set includes patients for whom microbiological response was assessed in the clinically-evaluable analysis set.

・ Methods of analysis

(1) Analysis for safety evaluation

The incidence of adverse reactions will be calculated for each event. Also, the factors affecting the occurrence of adverse reaction will be evaluated as necessary.

(2) Analysis for effectiveness evaluation

The clinical response rate in terms of the clinical effectiveness will be set as the primary effectiveness endpoint. The number of patients with "effective" and its proportion (clinical response rate) among the clinically-evaluable analysis set, and its 95% confidence interval will be calculated. The number of patients with eradication or presumed eradication, and its proportion (eradication rate) among the microbiological analysis set, and its 95% confidence interval will be calculated. The clinical response rate for each disease and its 95% confidence interval, and the eradication rate and its 95% confidence interval will be calculated. Also, an exploratory analysis on the factors affecting the effectiveness will be performed as necessary.

$$\text{Clinical response rate (\%)} = \frac{\text{Number of patients with "effective"}}{\text{Number of clinically-evaluable patients excluding "indeterminate"}} \times 100$$

$$\text{Eradication rate (\%)} = \frac{\text{Number of patients with "eradication" + "presumed eradication"}}{\text{Number of patients in the microbiological analysis set excluding "indeterminate"}} \times 100$$

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

7.8. Quality control

The site staff will explain the contents of the protocol, etc. to the investigator prior to the implementation of this study and ask the investigator to prepare a CRF based on medical charts.

7.9. Limitations of the research methods

The following matters are considered for this study:

1) Since no control group is set in the study, there is a limit to the judgment on whether or not a risk of developing AEs and adverse reactions increases due to the administration of the study drug.

2) The consideration for confounding factors may not be adequate because the background information may not be sufficiently obtained.

3) Since this is a study that collects the information described in medical charts, the set data may not be collected or there may be missing information.

7.10. Other aspects

N/A

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information and consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

In this study, the information will be collected by transcribing medical chart information described in routine medical practice. In doing so, the informed consent will not be required because the information collected from medical charts is anonymized and does not contain any information that identifies individual patients.

8.2. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs.

8.3. Institutional review board (IRB)/independent ethics committee (IEC)

In this study, the review by the IRB/IEC is not essential.

8.4. Ethical conduct of the study

This study is excluded from the patient since it includes the scope of application of the "MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171 dated December 20, 2004).

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The handling of each event in the case where the investigator becomes aware of any event concerning the safety information should be prescribed as follows:

For an event that needs to be reported to the Sponsor within 24 hours, the investigator must report it using the designated "Non-Interventional Study AE Report Form" (hereinafter referred to as "NIS AE Report Form").

At the initiation of study, the site staff should request the investigator to report events that need to be reported within 24 hours of awareness, and visit the investigator periodically during the study period to request for reporting.

The NIS AE Report Form will be handled as part of the CRF.

9.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the NIS AE Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy (EDP), exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the CRF	Reported on the NIS AE Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to this drug, including EDP, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see section "Serious adverse events" below)

Safety events must be reported to Pfizer within 24 hours of awareness of the event by the investigator as described in the table above **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For those safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information relevant to the event, such as concomitant medications and illnesses must

be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

9.2. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of this drug, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to this drug, the SAE also must be reported to Pfizer Safety.

9.3. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to this drug, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that this drug caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether this drug caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that this drug did not cause the event, this should be clearly documented on the CRF and the NIS AE Report Form.

9.4. Definitions of safety events

9.4.1. Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with this drug treatment or usage. Examples of AEs include but are not limited to the following:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;

- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from the following:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- EDP;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

9.4.2. Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

<u>Hospitalization</u>

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

9.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving EDP, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

EDP

An EDP occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) this drug, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to this drug (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to this drug prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposures during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with this drug, this information must be submitted to Pfizer, irrespective of whether an AE has occurred, using the NIS AE Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to this drug, in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AE Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy, in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for a SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs are as follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the EDP may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breast feeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to this drug, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to this drug the following minimum criteria constitute a medication error report:
    - An identifiable reporter;
    - A suspect product;
    - The event of medication error.

Overdose, misuse, extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

9.5. Single reference safety document

A Single Reference Safety Document (SRSD) refers to a document that contains the information on the known safety profile. The package insert of this drug will be the SRSD in this study. Pfizer Japan Inc. will evaluate the safety information reported by the investigator during the study period using the SRSD.

The investigator will also prescribe the drug and give the drug administration guidance based on the SRSD.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study results may be published during scientific meetings, in research paper, etc. for the purpose of providing proper use information, etc.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

11. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

The organizational system in this study is equivalent to that for the operations regarding the post-marketing study in the RMP. The director of the Post Marketing Study Strategy and Management will be responsible for post-marketing study.

12. NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS

1) Contractors

   [1] Operations concerning registration center
   Company name: EP-PharmaLine Co.,Ltd.
   Address: 3-27-12 Nishi-Ikebukuro, Toshima-ku, Tokyo

   [2] Reception of CRF and query form, data management, statistical analysis
   Company name: CAC EXICARE Corporation
   Address: 24-1 Hakozaki-cho, Nihonbashi, Chuo-ku, Tokyo

2) Scope of the outsourced operations

   Registration center, reception of CRF and query form, data management, and statistical analysis (operational jobs excluding the management of the study)

13. ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE STUDY RESULTS AND CRITERIA FOR DETERMINATION OF THE INITIATION

The RMP will be reviewed at the planned time of milestone including the followings:

- Necessity to change contents of the investigational plan should be discussed with the checking presence of new safety specifications.
- Necessity to develop actions to minimize risks for new safety specification should be discussed.
- Necessity to revise risk minimization activities for existing safety specifications should be discussed.

14. SCHEDULED TIMING OF MILESTONES AND THEIR RATIONALES FOR REPORTING OF STUDY IMPLEMENTATION STATUS AND EVALUATION OF OBTAINED RESULTS TO THE PMDA

[Planned time of milestone]

At the time of periodic safety report

[Rationale]

To review the safety information comprehensively

15. OTHER NECESSARY MATTERS

1) Amendment of the protocol

Based on the new knowledge to be obtained according to the progress of this study, the need for amendment of the protocol will be examined and the protocol will be amended if necessary. Also, the need for amendment of the protocol will be examined and the protocol will be amended even if the partial change in the dosage and administration or indication is approved during the reexamination period (except the case when the reexamination period is newly designated), etc.

2) Actions to be taken if any problem or question is observed

In the cases where the onset of any serious and unknown adverse reaction is suggested, a significant increase in the frequency of adverse reactions is observed, any problem is found in the effectiveness and safety of the drug compared to those prior to the approval, the onset of a different kind of adverse reaction is suggested, etc., the amendment of the package insert and implementation of a new special investigation or post-marketing clinical study should be considered.

PPD

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17. REFERENCES

None

18. LIST OF TABLES

19. LIST OF FIGURES

N/A

20. LIST OF STAND ALONE DOCUMENTS

N/A

21. ADDITIONAL INFORMATION

N/A