Tygacil® Injection
Drug Use Investigation

Protocol

Pfizer Japan Inc.

[redacted]

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[redacted]

INTRODUCTION

Tygacil® Injection (hereinafter referred to as "Tygacil") is the first glycylcycline antibacterial drug marketed in Japan; the drug was discovered by U.S. Wyeth Inc. (present Pfizer). Tygacil, by binding to the 30S ribosomal subunit, inhibits ribosome, and generates antibacterial activity by inhibiting the protein synthesis of bacteria.

In Japan, Tygacil obtained the marketing authorization in September 2012 for the indication of "Deep skin infections, chronic pyoderma, secondary infections associated with trauma, thermal burns, surgical wounds, etc., secondary infection of erosion or ulcer, peritonitis, intra-abdominal abscess, cholecystitis" with "Tigecycline-susceptible multiple resistant gram-negative bacteria (*Escherichia coli, Citrobacter spp., Klebsiella spp., Enterobacter spp., Acinetobacter spp.*)" as susceptible strains.

The drug use investigation of Tygacil Injection (hereinafter referred to as "Study") is intended to investigate the incidence of diseases, etc. due to adverse drug reactions of Tygacil by disease types, and to detect or confirm data concerning quality, effectiveness, and safety of Tygacil under actual use. The information obtained in this study will be used to provide Proper-Use Information, and to prepare documents for the Re-examination application. This study, therefore, 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 Affairs Law. Also, data concerning adverse drug reactions may be publicly posted in MHLW's "Pharmaceutical and Medical Device 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 drug reactions, gender, age (increment of 10 years), and other relevant information. Furthermore, the 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.

1 OBJECTIVES

This study is intended to assess the following information concerning Tygacil in daily medical practice.

- Adverse drug reactions which cannot be predicted from the post-marketing precautions of this drug
- Incidence of adverse drug reactions under the actual use, and
- Factors considered to affect the safety and effectiveness, etc.

Additionally, as the major investigation items, the incidence of the following adverse events will be confirmed.

- Thrombocytopenia
- Hepatobiliary disorder
- Pancreatitis
- Diarrhea and pseudomembranous colitis

2 PATIENTS

Patients who receive Tygacil will be included in this study.

The indications, dosage and administration, and target patients for this study are as follows. When using this drug, refer to the latest package insert of this drug.

INDICATIONS

(Susceptible strains)

Tigecycline-susceptible *Escherichia coli, Citrobacter spp., Klebsiella spp., Enterobacter spp., Acinetobacter spp.*

It should be limited to the strain being resistant to other antibacterial drug.

(Indications)

Deep skin infections, chronic pyoderma, secondary infections associated with trauma, thermal burns, surgical wounds, etc., secondary infection of erosion or ulcer, peritonitis, intra-abdominal abscess, cholecystitis

[Precautions related to INDICATIONS]

1. Tigecycline should be only use the strain showing resistant to two or more antimicrobial agents in beta - lactams, fluoroquinolones and aminoglycosides, and when other antibacterial drug showing antibacterial activity cannot be used.

DOSAGE AND ADMINISTRATION

For adults, 100 mg of tigecycline is initially administered via intravenous infusion over 30 to 60 minutes followed by 50 mg every 12 hours over 30 to 60 minutes.

3 STUDY SIZE

Target sample size is to be 100 subjects for safety analysis.

[Rationale]

The data collected from 100 subjects to whom Tygacil is administered should enable to detect and verify, with a probability of 95%, at least 1 subject in whom each adverse event with an incidence of 3% occurs, and thus enable to verify the post-marketing occurrences of major adverse drug reactions that occurred in domestic and overseas clinical studies (nausea, vomiting, diarrhea, abdominal pain, headache, hypoproteinaemia, ALT increased, and AST increased). Also, the target sample size of 100 subjects should enable to grasp the actual use status of Tygacil in clinical setting including patient backgroound and responder rate, in addition to safety evaluation.

Tygacil use is restricted to strains showing resistant to two or more antimicrobial agents in beta – lactams, fluoroquinolones and aminoglycosides, and when other antibacterial drug showing antibacterial activity cannot be used. The number of patients in whom multi-drug resistant Acinetobacter was reported in JANIS in 2011 was only 115, regardless of the presence of infection, and thus, it is estimated that Tygacil use will be extremely limited in actual clinical settings.

4 PLANNED INVESTIGATION PERIOD

The investigation period is from December 2012 to April 15, 2016.

(Case report forms should be collected for patients who complete the observation period and follow-up period as of April 15, 2016.)

For patients who do not complete the observation period and follow-up period as of April 15, 2016 or who are confirmed to use the targeted drug after this date, registration only should be continued until the condition for approval is lifted.

However, if collection of additional information is required for patients who continue registration only, case report forms should be collected for those who undergo observation and follow-up beyond the investigation period described above.

5 STUDY PROCEDURES

5.1 Study method

This study will be conducted with all patients surveillance system, and performed retrospectively.

At contract sites (including sites in which the contract is being concluded) as of April 15, 2016,

case report forms should be collected for patients who complete the observation period and follow-up period by April 15, 2016. For patients who do not complete the observation period and follow-up period as of April 15, 2016 or who are confirmed to use the targeted drug after this date, registration only should be continued. If collection of additional information is required for patients who continue registration only, the investigator will complete case report forms as requested by Pfizer Japan Inc. (hereinafter referred to as "Sponsor").

5.2 Data collection method

Registration and data for this study will be collected and recorded in the registration form and case report forms to be supplied by the Sponsor.

5.3 Patient registration

If a patient receives Tygacil, the investigator shall complete the patient registration form with site name, name of department, name of physician, the initials of the patient (as necessary), identification number, gender, date of birth, and date of Tygacil treatment commencement, and register such patient by sending it to the Registration Center by FAX.

[Registration Center]

FAX: PPD

5.4 Observation period

The observation period for this study will be from the commencement of Tygacil treatment (Day 1) to Day 14 at maximum; provided that a period of 28 days from the completion of the observation period will be considered as follow-up period during which, adverse events occurred will be recorded in the case report form.

5.5 Reminders concerning completing, revising, and reviewing of case report forms

(1) Completing

The investigator shall, upon confirming the study items, complete the case report form based on medical charts and other medical records including relevant test results, using a pen, ballpoint pen, or other inerasable means. Refer to a sample form to be provided separately for the details of procedures.

(2) Revising

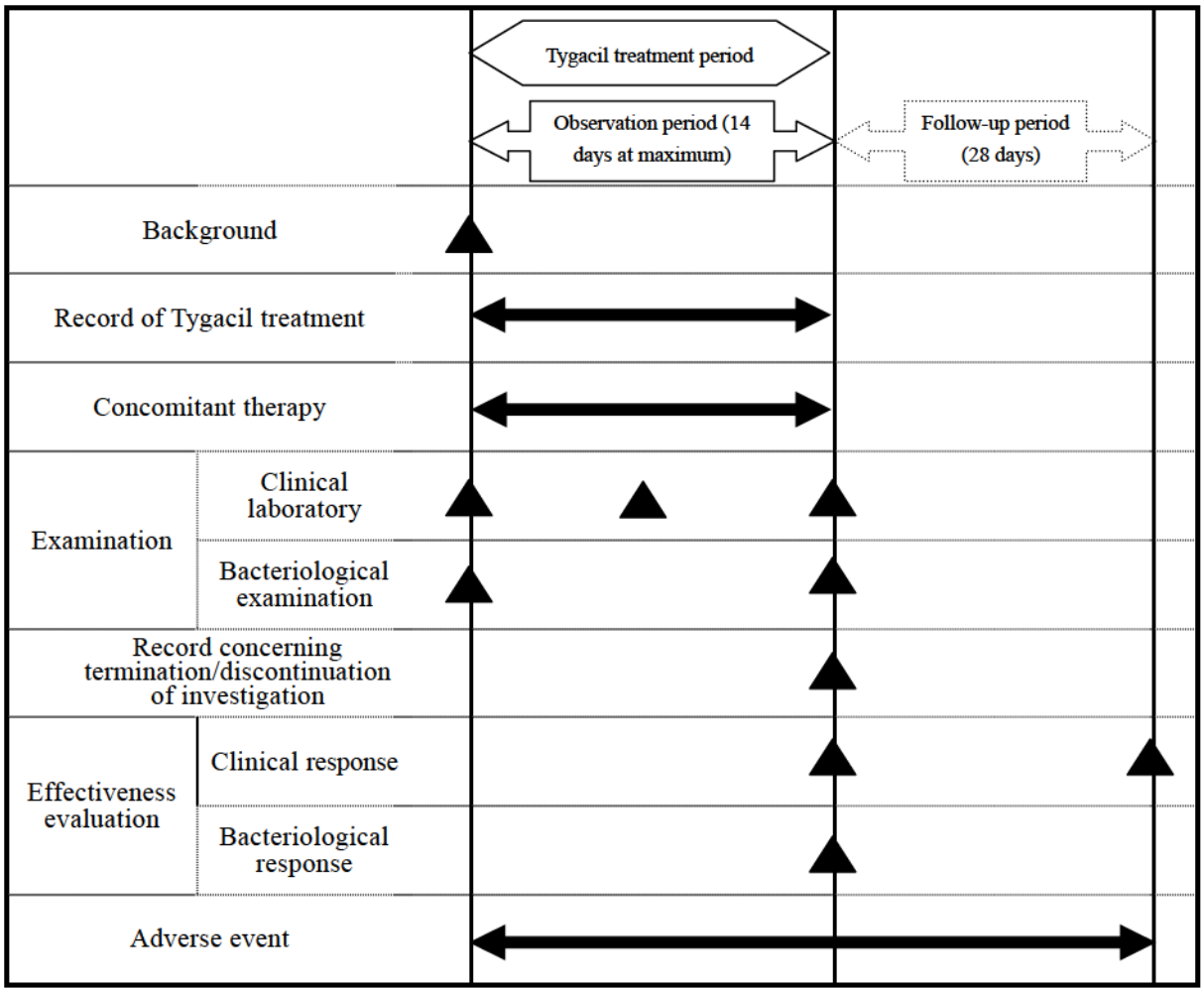
Corrections in the case report form should be struck out with a double line (=) with a

"correction seal" on the double line; the double line should be drawn so that the original contents prior to correction are legible. Upon receiving Sponsor's inquiry on the contents of the case report form, the investigator will again confirm the contents of the medical records, and as required, correct relevant sections in the case report form. In addition, a correction concerning effectiveness and safety must be, in principle, indicated with the reason for such correction, together with the date on which the correction is made.

(3) Reviewing

Upon completion of all entries and corrections of the study items, the investigator shall once again review the information in the case report form and associated query forms, and sign or seal/name these forms.

6 INVESTIGATION ITEMS AND SCHEDULE



6.1 Background

(1) The following information at the commencement of Tygacil treatment will be recorded in the case report form:

[1] Gender

[2] Date of birth (age, if the date of birth cannot be disclosed)

[3] Inpatient/outpatient status

[4] Height

[5] Weight

[6] Disease subject to study (infection for which Tygacil is used)

- Name of disease
- Severity

[7] Medical history (past history and concurrent illness other than the underlying disease subject

to study*)

・Presence/absence of liver functional impairment, renal functional impairment

・Names of diseases/syndromes other than the above, and whether such diseases are past or current

[8] Reason for deciding to use Tygacil (select from among below)

・Patient did not respond to other antibacterial drugs (the name(s) of previous antibacterial drugs to which the patient did not respond should also be recorded)

・The causative bacteria were resistant to the following drug(s) (Details should be described in the bacteriological examination section):

Beta-lactam antibacterial drugs

Fluoroquinolone antibacterial drugs

Aminoglycoside antibacterial drugs

・Other drug with antibacterial activity could not be used as determined by the physician (reason for such decision should also be recorded)

・Others (specific reason(s) should be described)

*: Chronic diseases (including allergy), diseases requiring medical treatment, diseases/disorders accompanied by surgery, hospitalization, and/or subsequent complications, or any other diseases/syndromes determined problematic are applicable herein; of which, those occurred prior to the commencement of Tygacil treatment will be considered as "Past history", and those concurrent at the time of treatment will be considered as "Concurrent illness."

Pregnancy status at the completion of the observation period, and in case pregnancy is confirmed, the actual/expected date of delivery should also be recorded.

6.2 Targeted drug use record

The following Tygacil drug use information will be recorded:

[1] Date of administration

[2] Dose

[3] Time the infusion is commenced

[4] Duration of infusion

6.3 Concomitant therapy

(1) Drug therapy

The following information concerning all concomitant drug therapy each patient receives

during the observation period should be recorded.

Also, any drug(s) used for the treatment of an adverse event should be recorded.

[1] Drug name (product name)

[2] Route of administration

[3] Date of treatment commencement

[4] Presence/absence of treatment for adverse event

(2) Non-drug therapy

The following information concerning all non-drug concomitant therapy implemented during the observation period should be recorded.

Also, any non-drug concomitant therapy used as treatment for an adverse event should be recorded.

[1] Name of therapy

[2] Date of treatment commencement

[3] Presence/absence of treatment for adverse event

6.4 Tests/clinical laboratory tests

(1) Clinical laboratory tests

The following parameters of clinical laboratory tests performed at the commencement of Tygacil treatment, during and at the end of the observation period should be recorded.

[1] Laboratory parameters

- White blood cell count
- Platelet count
- Hemoglobin count
- Total protein
- Total bilirubin
- AST
- ALT
- ALP
- γ-GTP
- CRP
- Amylase
- Lipase
- Serum creatinine
- BUN
- Prothrombin time
- Activated partial thromboplastin time (APTT)
- Urine bilirubin

[2] Unit

[3] Test date

[4] Test results

(2) Bacteriological examinations

The following information concerning the causative bacteria, for which Tygacil was used, should be recorded for its status at the commencement of Tygacil treatment, at the end of

observation period, and at the time the disease was determined to be "cure."

[1] Specimen

[2] Name of the strain

[3] Date of specimen collection

[4] Bacteria count (-, +, ++, +++)

[5] Susceptibility to Tygacil and other antibacterial drugs (for other antibacterial drugs, only the data at the commencement of Tygacil treatment shall be collected)

If diarrhea occurs in the patient after commencement of Tygacil treatment, the results of the following tests should be recorded, if conducted.

[6] Bacteriologic culture test for *Clostridium difficile*

[7] Antigen test for *Clostridium difficile*

6.5 Record of completion/discontinuation of observation period

If the observation period is 14 days or shorter, the reason should be selected from among the below. If "Adverse event" or "Death" is selected, the details should also be recorded in the adverse event section.

[Completion]

- Cure

[Reason for discontinuation]

- Insufficient clinical responses
- Adverse event
- Death (date of death)
- Lost to follow-up
- Transfer to another hospital/department (name of medical institution/department)
- Others

6.6 Effectiveness evaluation

(1) Clinical response

[1] Clinical response at the end of observation period

Clinical response to the treatment by Tygacil should be evaluated on the day of completion of the observation period, and the laboratory and clinical findings that contributed to the effectiveness assessment should be recorded.

- Effective
- Ineffective

・Indeterminate (reason(s) should be recorded)

Clinical response should be evaluated based on laboratory and clinical findings; bacteriological response should be excluded.

Any findings that are considered clinically problematic compared to the baseline should be recorded in detail in the adverse event section.

[2] Clinical response at the time the disease is judged to be "cure."

Whether the disease is recovered or not should be judged within 28 days from the completion of Tygacil treatment.

・Cured

・Ineffective

・Indeterminate (reason(s) should be recorded)

(2) Bacteriological response

Bacteriological response should be evaluated on the day of completion of the observation period, and the results thereof should be recorded.

・Eradication

・Presumed eradication

・Colonization

・Persistence

・Presumed persistence

・Microbial substitution

・Superinfection

・Relapse

・Indeterminate

6.7 Adverse event

The status of adverse events from the commencement of Tygacil treatment to 28 days after completion of the observation period (or treatment discontinuation) should be confirmed and the following information should be recorded. Upon occurrence of any adverse event, the investigator shall provide appropriate treatment, promptly report to the Sponsor, and if a causal relationship with Tygacil cannot be ruled out, follow up on the course and outcome as appropriate.

Also, occurrence of a serious adverse drug reaction, an unexpected adverse drug reaction, or other adverse drug reactions should be separately investigated in detail if determined necessary by the Sponsor.

[2] Presence/absence of adverse event

[3] Name of adverse event

[4] Date and time of occurrence (only the observation period)

[5] Intervention

[6] Seriousness

[7] Outcome

[8] Causal relationship

[If the adverse event is associated with abnormal 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

Note: Adverse events are any and all unfavorable events (including clinically significant abnormal changes in laboratory tests) occurring in patients after starting the target drug treatment regardless of their causal relationship. Serious adverse events are any unfavorable medical occurrences that result in death, are life-threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which represent significant health hazards.

6.8 Major investigation items

(1) Thrombocytopenia

[Rationale for setting]

Thrombocytopenia has been reported in patients with severe systemic infection for which Tygacil is indicated as well as in patients receiving various other drugs, thus adverse drug reaction status of thrombocytopenia was selected as a major investigation item.

[Investigation method]

Presence/absence and the incidence of thrombocytopenia and adverse events related to thrombocytopenia will be confirmed. Furthermore, platelets and hemoglobin count before the commencement and at the completion (discontinuation) of Tygacil treatment will be collected to investigate the changes in platelet count before and after Tygacil treatment.

(2) Hepatobiliary disorder

[Rationale for setting]

Tygacil is a drug excreted in the bile, and also patients with severe systemic infection for which Tygacil is indicated are usually vulnerable to hepatobiliary disorder, and therefore, adverse drug reaction status of hepatobiliary disorder was selected as a major

investigation item.

[Investigation method]

Presence/absence and the incidence of hepatobiliary disorder and adverse events related to hepatobiliary disorder will be confirmed. Furthermore, ALT, AST, ALP, total bilirubin, and urinary bilirubin before the commencement and at the completion (discontinuation) of Tygacil treatment will be collected to investigate the changes in these values before and after Tygacil treatment.

(3) Pancreatitis

[Rationale for setting]

Effect of tetracycline antibacterial drugs on the pancreas such as increased amylase/lipase and acute pancreatitis has been reported, thus, adverse drug reaction status of pancreatitis was selected as a major investigation item.

[Investigation method]

Presence/absence and the incidence of pancreatitis and adverse events related to pancreatitis will be confirmed. Furthermore, amylase, lipase, and γ-GTP before the commencement and at the completion (discontinuation) of Tygacil treatment will be collected to investigate the changes in these values before and after Tygacil treatment.

(4) Diarrhea and pseudomembranous colitis

[Rationale for setting]

Diarrhea related to *Clostridium difficile* and diarrhea accompanying pseudomembranous colitis have been reported with various antibacterial drugs, thus, adverse drug reaction status for diarrhea and pseudomembranous colitis were selected as major investigation items.

[Investigation method]

Presence/absence and the incidence of diarrhea and pseudomembranous colitis will be confirmed. Also, relevant information including the dosage of Tygacil, background such as concurrent illness, and concomitant medications should be collected, and if diarrhea or pseudomembranous colitis occurs, bacteriologic culture or antigen test for *Clostridium difficile* should be performed, and the results should be evaluated.

7 STATISTICAL ANALYSIS PLAN

7.1 Analysis set

The safety analysis set included patients who received Tygacil as reported by the physicians. The effectiveness analysis set shall, in accordance with a statistical analysis plan separately

prepared, include all evaluable patients (patients determined to have been appropriately evaluated).

7.2 Method of analysis

(1) Analysis for safety evaluation

In the safety analysis set, occurrence/incidence of adverse drug reactions (percentage of patients with adverse events for which the causal relationship with this drug cannot be ruled out) will be set as primary analysis items. Also, factors that may have affected the occurrence of adverse drug reactions will be evaluated, as appropriate.

Major investigation items (thrombocytopenia, hepatobiliary disorders, pancreatitis, diarrhea, and pseudomembranous colitis) will be tabulated/analyzed for occurrence/incidence of adverse drug reactions and changes in associated laboratory values for safety assessment.

(2) Analysis for effectiveness evaluation

In effectiveness analysis set, [the total number of patients who clinically responded divided by the total number of patients evaluable for effectiveness] will be set as a primary analysis item. In addition, bacteriological response will be evaluated. An exploratory analysis including that on factors that may have affected the effectiveness will be performed, as appropriate.

8 DISSEMINATION OF THE RESULTS

The results of this study shall be disseminated with one of the following that are applicable. In addition, as required, the results may be published during scientific meetings, in research paper, etc. for the purpose of providing proper-use information, etc.

- Studies registered to www.clinicaltrials.gov (ClinicalTrials.gov), regardless of the reason for such registration.
- Studies other than the above with results that are of scientific and medical importance as determined by Sponsor.

The timing of public release is dependent on the presence of any country with approval of the product at the time of completion of the study.

Any study involving an already-approved Pfizer product in any country will require Pfizer to publicly release the results within 1 year of the finalization of last-patient last-visit data.

Literature references to be used will be limited to those widely recognized and accessible through searchable literature databases.

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10 REFERENCES

Attachment 1: Adverse events report