For application of re-examination

TORISEL 25 mg Injection

Special Investigation

— All patient surveillance —

Protocol

[redacted]

Pfizer Japan Inc.

Date of preparation: August 24, 2010, Version 1
Date of revision: February 2, 2011, Versions 2
Protocol ID: B1771015

[redacted]

INTRODUCTION

TORISEL 25 mg Injection (hereinafter called this drug) is a m-TOR inhibitor. This drug acts by inhibiting mTOR (mammalian target of rapamycin), which is a kinase regulating the growth and proliferation of cancer cells. It was granted the marketing authorization in Japan on July 23, 2010 with an indication of metastatic and/or unresectable renal cell carcinoma.

Special Investigation of TORISEL 25 mg Injection - All patient surveillance - (hereinafter called this study) is intended to confirm the effectiveness and safety of this drug in daily clinical settings, examine the onset state of adverse events and potentially influencing factors (particularly, those designated as major investigation items), and examine the onset state and potential onset risk factors of interstitial lung disease. The information obtained in this study shall 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, pertinent to which 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 reactions, gender, 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 investigators, sites, and other personal information be subject to such disclosure, nor will it be posted or disclosed in any form or shape.

1 OBJECTIVES

The objective of this study is to assess the following subject matters in patients treated with TORISEL 25 mg Injection (hereinafter called this drug) in post-marketing actual use conditions, thereby providing proper-use information.

(1) To confirm the effectiveness and safety of this drug under actual use conditions
(2) To examine the onset state of adverse events and potentially influencing factors (particularly, major investigation items)
(3) To examine the onset state and potential onset risk factors of interstitial lung disease

[Conditions for approval]

A drug use investigation must be conducted with all the patients treated with this drug until the data from a specified number of cases are accumulated after the marketing of this drug in order to understand the background information on patients treated with this drug, collect the data on the safety and effectiveness of this drug as early as possible, and take necessary measures to ensure the proper-use of this drug.

2 PATIENTS

This study will be conducted with all patients treated with this drug in a specific period of time. The indications and dosage and administration of this drug are described below.

[Indications]
Metastatic and/or unresectable renal cell carcinoma

[Precautions Regarding Indications]
1. The efficacy and safety of TORISEL as postoperative adjuvant chemotherapy has not been established.
2. The selection of patients in whom to administer TORISEL must be performed after thorough consideration of the efficacy and safety data based on understanding of information detailed in "Clinical Studies*".
   * Refer to the [Clinical Studies] section in the package insert.

[Dosage and Administration]
The usual adult dosage is temsirolimus 25 mg once weekly, to be administered via intravenous infusion over 30 - 60 minutes. The dosage is to be appropriately reduced according to patient's condition.

[Precautions regarding dosage and administration]
1. The efficacy and safety of TORISEL in combination use with other anti-malignant tumor agents including cytokine preparations have not been established.
2. When interstitial lung disease occurs, interrupt/discontinue administration depending on the symptoms and severity with consideration of the following criteria:

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Criteria for interruption or discontinuation in case of interstitial lung disease

Symptom	Intervention
Asymptomatic. Only abnormal imaging findings are observed.	Continue to administer.
Mild clinical symptoms [Note)] (not interfering activity of daily living)	Interrupt administration until the symptoms recovered.
Severe clinical symptoms [Note)] (interfering with activity of daily living and need oxygen therapy)	Discontinue
Aggravation of clinical symptoms and pulmonary diffusing capacity decreased	
Underlying pulmonary disease, with changes in clinical or image findings are observed	

Note: Dyspnea, cough, etc.

3. If severe adverse reactions (Grade 3 or severer) occur other than interstitial lung disease, interrupt administration of TORISEL until resolution of the adverse reaction. If the adverse reaction is resolved within 3 weeks, administration can be resumed at a reduced dose by one level (reduction levels should proceed as follows: initial dose 25 mg -> 20 mg-> 15 mg -> 10 mg).
4. To avoid infusion reactions, an antihistamine (e.g., d-chlorpheniramine maleate, diphenhydramine hydrochloride, etc.) should be administered prior to the administration of TORISEL. If infusion reactions occur, stop administration immediately.
5. When administering TORISEL, do not use infusion kits containing DEHP [di-(2-ethylhexyl) phthalate] as a plasticizer.
6. An in-line filter with a pore size of not greater than 5 μm should be used for TORISEL infusion.
7. Dose reduction should be considered for patients with severe hepatic function disorder.

3 STUDY SIZE

All the patients treated with this drug will be included in the all patient surveillance to be conducted for a specific period of time.

- Target number of cases: 600 cases
- Target number of cases observed: 300 cases treated for 12 weeks or longer (300 cases with Booklet 03 case report form)
  (Cases who discontinued the drug before 12 weeks will also be included.)

[Rationale]

The incidence of all the adverse events included in the major investigation items of this study was 1.0% or higher in the drug group of the foreign phase 3 clinical study (304-WW Study). Assuming that the true incidence of an adverse event (particularly an adverse event included in the major investigation items) is 1.0%, 300 cases are required to observe at least 1 case with the event at a probability of at least 95%. The incidence of interstitial lung disease was 17.1% (14/82) in the multinational (Asian) phase 2 clinical study (2217-AP Study).

Assuming that the true incidence of interstitial lung disease is 17.1%, at least 40 cases with the disease can be observed at a probability of at least 95%.

Further, clinical study results showed that interstitial lung disease occurred on Week 4 after the start of the drug or later, and that, in rare cases, some adverse events had an increased incidence or delayed onset as the administration period was prolonged. Considering these results, it was decided to set a target that this study would include 300 cases treated with this drug for 12 weeks or longer.

Clinical study results showed that this drug could be continued for 12 weeks or longer in about 60% of the whole treated cases, with a discontinuance/drop-out rate at 12 weeks of about 40%. Considering that this study will be conducted under actual use condition, it is assumed that the discontinuance/drop-out rate at 12 weeks in this study will be increased by 10% to 50%. That is, it is assumed that this drug will be continued for 12 weeks or longer (the Booklet 03 case report form will be collected) in 50% of the cases included in this study.

Therefore, this surveillance was planned to register 600 cases to collect 300 cases treated with this drug for 12 weeks or longer. In addition, because cases which discontinue the drug before 12 weeks will be included in the study, the case report form will be collected from them to evaluate safety and effectiveness.

4 PLANNED INVESTIGATION PERIOD

Study period*: September 2010 (launch of this drug) to August 2012 (2 years)

Registration period: September 2010 (launch of this drug) to

The cases treated with this drug after the initial 600 cases will be registered, but not studied.

* However, this study will be conducted until March 2014 when the separate Special Investigation on long-term use is included (cumulative study period: 3 years and 6 months).

5 STUDY PROCEDURES

5.1 Study method

This study will be conducted with all the patients treated with this drug until the data from a specified number of cases are accumulated after the marketing of this drug in order to understand the background information on patients treated with this drug, collect data on the safety and effectiveness of this drug as early as possible, and take necessary measures to ensure the proper-use of this drug. This study will be conducted as all patient surveillance system at sites with investigators who have sufficient knowledge and experience about drug therapy for renal cancer.

(1) Conduct of prior explanation

Medical representatives (MRs) will explain the safety and effectiveness of this drug to investigators and pharmacists expected to use the drug using the materials for providing safety information.

[Materials for providing safety information]

- Package insert
- Explanation to "Precautions for Use" of new drugs
- Interview Form
- Proper-use guide
- Summary of general product information

(2) Study contract

After the prior explanation, a contract will be made with each site on this study. A specific contract form of a site, if any, will be used. This drug will be supplied to each site after the contract with the institution is made.

5.2 Data collection method

In this study, the case report form provided by the sponsor will be used to collect data when the sponsor asks sites to use it. When the sponsor asks sites to use the specific case report form to collect data, the investigator in each site will readily fill in the form and submit it to the sponsor.

5.3 Patient registration

(1) Registration procedure

The investigator will complete the registration form on patients treated with this drug provided by sponsor, and submit the form to Patient Registration Center via FAX at treatment.

[TORISEL Patient Registration Center]
Fax number: 0120-655-781 (available 24 hours)
Business hours: 9:00 to 18:00*
(except for Saturdays, Sundays, National Holidays, and New Year Holidays)
*FAX transmission after 17:30 will be responded by 9:30 on the following business day.

(2) Case registration

After the patient was registered, "the announcement of the patient registration" will be sent to the investigator by FAX. Investigator will save the announcement in the site.

If there is something to be confirmed found in the registration form, confirmation will be requested with the investigator. In the case of confirmation, "request form of confirmation" and "registration form (copy)" will be sent from the Registration Center to the investigator by FAX.

(3) Confirmation of registered case

At the end of the registration period, each investigator will confirm that all his/her cases treated with this drug are listed in the "TORISEL Special Investigation Registration List," and submit it to MR in charge with his/her signature or print of his/her name with his/her seal.

When an investigator finds a case treated with the drug, but not registered in the list, the investigator will readily register the case.

5.4 Observation period

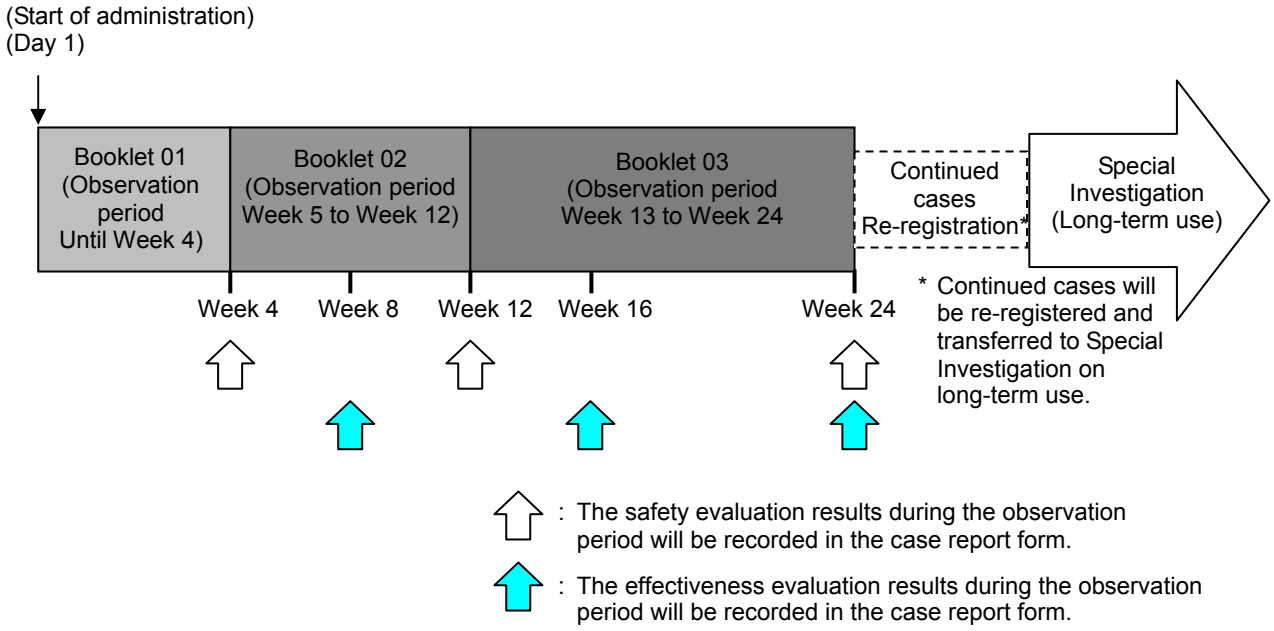
The observation period for this study will be set until Week 24 after the start of administration (cases treated with the drug for more than 25 weeks will be included in the separately planned Special Investigation on long-term use and observed for up to 96 weeks after the start of administration)

Clinical evaluation of tumor: Weeks 8, 16, and 24. For discontinued cases, if the clinical evaluation of tumor is not performed within 4 weeks prior to discontinuation, clinical evaluation of tumor will be performed at the time of discontinuation.

Adverse events: Until Week 24 after the start of administration. If the drug is discontinued before Week 24, observe until Day 28 after the discontinuation of administration.

This study will be conducted using a case report form divided into separate booklets. The results during the following observation periods will be recorded in the different booklets of the case report form.

Booklet	Observation period
Booklet 01	Start of administration to Week 4 (Day 28)
Booklet 02	Week 5 (Day 29) to Week 12 (Day 84) after start of administration
Booklet 03	Week 13 (Day 85) to Week 24 (Day 168) after start of administration



Observation period and evaluation time points for each booklet of case report form

[redacted]

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

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

(2) When the investigator receives an inquiry from Pfizer Japan Inc. (for data confirmation), he/she will reconfirm the above medical records and, if necessary, correct and re-submit the case report form. When the investigator corrects a part of the case report form, he/she will draw a double line on the part so that the original entry is kept visible and put a correction seal. When the confirmation investigator corrects a part related to evaluation of effectiveness or safety, in principle, he/she will record the reason and date of correction.

6 INVESTIGATION ITEMS AND SCHEDULE

The investigator will conduct the study according to the following schedule of observation. After the conclusion of the study contract, the investigator will register patients who meet the registration conditions, check their data including the background information at the start of administration, and fill in the case report form (at patient registration and at the start of administration). In the observation period, the investigator will check their follow-up data at the end of the observation period of each booklet of the case report form or at discontinuation when the drug is discontinued, record the data to the case report form and submit it to the sponsor.

[Observation schedule]

		Observation and evaluation time points			
		At the start of administration	Starting date of administration to Week 4 (Day 28)	Weeks 5 to 12 after start of administration	Weeks 13 to 24 after start of administration
Registration information	ID number, patient initials, gender, date of birth (age), scheduled date to start administration, and availability of pre-treatment chest CT	●			
Patient background		●			
Clinical history		●			
Prior treatment history		●			
Record of TORISEL treatment			◄———	———	———►
Concomitant therapy (drug therapy)			◄———	———	———►
Concomitant therapy (non-drug therapy)			◄———	———	———►
Examination (chest CT)		●	●	●	●
Examination (chest X-rays)		●	●	●	●
Examination (clinical laboratory testing)		●	●	●	●
Effectiveness evaluation*				Week 8	Week 16 Week 24
Pregnancy status			●	●	●
Patient summary (continuation/discontinuation status)			●	●	●
Adverse events			◄———	———	———►
Detailed information on adverse events related to interstitial lung disease (Attachment: detailed case report form)			◄———	———	———►

* For discontinued cases, if the clinical evaluation of tumor is not performed within 4 weeks prior to discontinuation, clinical evaluation of tumor will be performed at the time of discontinuation.

6.1 Background

(1) The following information will be recorded to the registration form at the start of this drug administration.
- [1] ID number
- [2] Patient initials (as required)
- [3] Gender
- [4] Date of birth (age)
- [5] Scheduled date to start administration
- [6] Availability of pre-treatment chest CT

(2) The following information will be recorded to the case report form at the start of this drug administration.
- [1] Height, body weight, and hospitalization status
- [2] Disease to be studied and date of diagnosis

[3] State of tumor (TNM classification, metastatic status at the start of this drug, and histopathological diagnosis)
[4] Performance status (ECOG PS)
[5] MSKCC risk classification (LDH, albumin, calcium, and Karnofsky performance status at the start of administration); the other items of the MSKCC risk classification will be calculated from the patient background information and laboratory test results.
[6] Other patient background information (smoking history, familial history of diabetes, lung surgery history, prior use of steroids, occupational and environmental exposure to asbestos and pneumoconiosis, prior administration of high concentration oxygen to treat respiratory diseases, and history of drug and non-drug allergies
[7] Clinical history (history of diseases and complications)
[8] Presence/absence of hepatic/renal dysfunction
[9] Prior treatment history (history of surgery, radiotherapy, other non-drug therapy, and drug therapy for renal cell cancer)

6.2 Targeted drug use record

The following TORISEL use information will be recorded for each observation period.

[1] Date of administration
[2] Dose
[3] Reason for dose change

6.3 Concomitant therapy

6.3.1 Drug therapy

The following information will be recorded in each booklet of the case report form for all the drugs administered from the start date of the observation period to the date of safety evaluation. If an adverse event is noted, the drugs used during the period from the start day of the observation period to the onset of the adverse event and medications used for treatment of the adverse event should also be recorded.

[1] Drug name (product name)
[2] Administration route
[3] Daily dosage
[4] Daily dosing frequency
[5] Administration period
[6] Reason for the administration

6.3.2 Non-drug therapy

The following information will be recorded in each booklet of the case report form for the non-drug therapy given from the start date of the observation period to the safety evaluation date. If an adverse event is noted, the non-drug therapy used during the period from the start day of the observation period to the onset of the adverse event and non-drug therapy used for treatment of the adverse event should also be recorded.

[1] Name of therapy
[2] Therapeutic period
[3] Reason for the therapy

6.4 Tests / Clinical laboratory tests

[1] Chest CT examination
[2] Chest X-ray examination
[3] SpO_2, KL-6, SP-D, SP-A
[4] Hemoglobin, white blood cell count, white blood cell differentiation (neutrophil count), and platelet count
[5] AST, ALT, total bilirubin, and ALP
[6] Total cholesterol and triglyceride
[7] Fasting blood sugar and HbA1c
[8] BUN and serum creatinine
[9] Potassium and phosphoric acid
[10] CRP

6.5 Effectiveness evaluation

6.5.1 Clinical evaluation of tumor

Clinical evaluation of tumor will be performed at Weeks 8, 16, and 24 after the start of administration. The presence/absence of the target, non-target, and new lesions will be evaluated at each evaluation time point. The evaluation will be performed using the following 4 classes with reference to the "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) - Japanese Translation JCOG Version."

Complete response	(CR)	Disappearance of all target regions
Partial response	(PR)	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive disease	(PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started
Stable disease	(SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

6.6 Patient background (at the completion)

The pregnancy status between the starting date of administration and safety evaluation date and actual/expected date of delivery will be recorded (for female patients only).

6.7 Patient summary (reason for discontinuation)

Continuation or discontinuation of the treatment with this drug is determined on the safety evaluation date. When it is determined that the treatment with this drug cannot be continued, the major reason of discontinuance will be selected from the following options and recorded (multiple selection not permitted). Appropriate data will be recorded to the adverse event section of the form when any of the following options is selected: [2] adverse event, [3] abnormal laboratory test value, or [4] patient's death.

[1] Insufficient clinical effectiveness
[2] Adverse event
[3] Abnormal laboratory test value
[4] Patient's death (date of death)

[5] Lost to follow-up (reason)
[6] Others (specify the reason, such as treatment completed because of cure)

6.8 Adverse event

To evaluate safety, the onset of adverse events after the start of the drug administration will be investigated and the following information (1) to (9) will be recorded. In principle, each adverse event will be followed until each safety evaluation date. If an adverse event occurs, the investigator will give appropriate treatment, readily notify the sponsor as specified in the "Adverse Event Reporting" (attachment), and, in principle, follow its outcome and clinical course until its symptom is resolved. Particularly, the investigator will call by phone the following contact number within 24 hours "when a serious adverse event occurs", "when a patient or his/her partner becomes pregnant or is found to be pregnant during the treatment with this drug regardless of the onset of adverse events", or when the investigator knows any additional information on the adverse event or pregnancy. For details, refer to the "Adverse Event Reporting" (attachment).

Contact number in case of serious adverse event		
[TEL]	0120-099-526	(toll-free)
[Business hours]	9:00 to 18:00	(available every day of the year)

In addition, a detailed study will be separately conducted for intrauterine exposure, serious adverse reactions, or adverse reactions not listed in the package insert, etc., if deemed necessary by the sponsor.

[1] Date of safety evaluation
[2] Presence/absence of adverse events
[3] Adverse event name (disease or symptom name)
[4] Date of onset
[5] CTCAE v4.0 Grade
[6] Treatment
[7] Seriousness
[8] Current outcome of adverse event
[9] Causal relationship

Important: 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.

Supplementary information:

The progress of the target malignant tumor will not be recorded as an adverse event. However, any malignant tumor that reaches a lethal outcome during the observation period has to be recorded as an adverse event. When a patient starts a new treatment, the reportable period of the event will end when the new treatment is started.

6.8.1 Detailed information on adverse events related to interstitial lung disease

When interstitial lung disease occurs, the attachment (detailed case report form) will be recorded separately. The sponsor will request the site to provide the results of chest CT and/or chest X-rays (images or data).

6.9 Major investigation items

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

[1] Interstitial lung disease
[2] Dyspnea
[3] Diabetes/hyperglycaemia
[4] Hypersensitivity reaction
[5] Diarrhoea
[6] Hypophosphataemia
[7] Hypokalaemia
[8] Hypercholesterolaemia/hyperlipidaemia
[9] Infections
[10] Intracerebral hemorrhage
[11] Wound healing abnormal
[12] Mucositis related adverse events
[13] Skin disorder
[14] Acute renal failure
[15] Gastrointestinal perforation
[16] History of infection with hepatitis B, tuberculosis, or herpes zoster

For patients who develop any adverse event in the above major investigation items, a separate detailed survey as specified in the attachment will be conducted if deemed necessary by the sponsor.

7 STATISTICAL ANALYSIS PLAN

7.1 Analysis Set

As a rule, the safety analysis set will include patients who satisfy the eligibility criteria and confirmed to be treated with this drug at least once. As a rule, the effectiveness analysis set will include patients who are evaluable for effectiveness (patients considered to have received appropriate evaluation). The details of the analysis sets will be specified in a statistical analysis plan.

7.2 Method of Analysis

7.2.1 Analysis for safety evaluation

The following items will be mainly analyzed in the safety analysis population.

The analytical method for the major investigation items will be specified in the statistical analysis plan, in accordance with the objective of analysis.

[1] Onset state of adverse events/adverse reactions (particularly the major investigation items)

[2] Onset state of adverse reactions and potential influencing factors (particularly the major investigation items)

[3] Safety in patients with special background (pediatric patients, elderly patients, pregnant women, patients with renal or hepatic dysfunction)

[4] Safety in patients with hepatic dysfunction (including the comparative examination with results from the foreign phase 1 clinical study)

[5] Onset state of interstitial lung disease (including asymptomatic cases with imaging findings of the disease)

[6] Potential risk factors of interstitial lung disease

[7] Characteristics of interstitial lung disease (imaging findings, onset timing, duration, and breakdown by severity)

[8] List of clinical course of interstitial lung disease (contents of treatment, response to treatment, and outcome) and clinical course after the drug is restarted (presence/absence of recurrence/exacerbation, etc.)

[9] Onset state of various related events suspected of causing interstitial lung disease (pneumonitis/lung infiltration and pulmonary fibrosis, etc.)

7.2.2 Analysis for effectiveness evaluation

The response rate and clinical benefit rate as shown below will be used as main analytical items in the effectiveness analysis set. An CCI [redacted] analysis including the examination of factors influencing effectiveness will be performed, as required.

[1] Response rate (rate of CR + PR)

[2] Clinical benefit rate (Rate of cases with CR + PR + SD maintained for 24 weeks or longer)

8 DISSEMINATION OF THE RESULTS

Pfizer Japan will comply with a responsibility to publish the present study results by posting them on ClinicalStudyResults.org. Pfizer Japan will disclose the results of the study that meets either of below. As needed, Pfizer Japan will publish the study results (journals or at the academic society meetings) to provide the proper-use information of this drug.

- The study registered to www.clinicaltrials.gov (ClinicalTrials.gov) by Pfizer Japan, regardless of the reason for such registration.
- Other than above, the study whose results are considered important by Pfizer Japan from the scientific or medical view point.

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 Japan to publicly release the results within 1 year of the finalization of last-patient last-visit (LSLV) data.

Pfizer Japan will post the following items in ClinicalStudyResults.org.

- Title of post-marketing surveillance protocol, developmental stage, and target disease
- Labeling of approved product
- Outline of study results
- References to published papers
- Disclaimer

The study results will be posted on ClinicalStudyResults.org (Pharmaceutical Research and Manufacturers of America [PhRMA] website synopsis [PWS]) according to the form specified in ICH E3. When an intended posting of study results on ClinicalStudyResults.org may interfere with a planned posting of other study results, a statement that the publication of the results is reserved will be posted instead of the outline of the study results. The posting period of the statement will be until the publication of the study results or 2 years after the completion of the study, whichever comes first.
Literature references to be used will be limited to those widely recognized and accessible through searchable literature databases.

9 CONTACT INFORMATION

[redacted]

10 REFERENCES

Package Insert of TORISEL 25 mg Injection
Attachment: Adverse Event Reporting

[redacted]