Drug Use Investigation for Arzerra
Chronic Lymphocytic Leukemia (CLL)

1. Study Objectives

The safety and efficacy of Arzerra® Injection for Intravenous Infusion (hereinafter referred to as "Arzerra") will be investigated under the conditions of actual use after marketing to identify the status of occurrence of adverse drug reactions (ADRs) and factors affecting the safety and efficacy of Arzerra.

<Priority study items>
Infusion reactions*, infections, tumour lysis syndrome, hematotoxicity, intestinal obstruction, skin disorder, cardiac disorder, blood pressure decreased, hepatic dysfunction/jaundice, renal disorder, and interstitial lung disease.
* For its definition, refer to Section 11.4).

[Conditions for approval]
The number of patients enrolled in the clinical trials of Arzerra in Japan was quite limited. Therefore, until data from a certain number of patients after marketing are accumulated, a drug use investigation covering all patients receiving Arzerra should be conducted to identify demographic information on patients using Arzerra. In addition, the safety and efficacy of Arzerra should be collected as early as possible, to take necessary measures for the proper use of Arzerra.

2. Planned Sample Size and Its Rationale

1) Number of patients planned for the investigation: 300 patients with relapsed or refractory CD20-positive chronic lymphocytic leukemia (CLL) (number of patients to be analyzed).

2) Rationale:
The incidences of the priority study items are considered to be roughly ≥1%. Therefore, to allow the detection of at least one case of each event with a probability of at least 95%, the number of patients to be analyzed is set at 300.
From the aspect of identification of the conditions of actual use, patients who received Arzerra, regardless of the number of doses, and from whom safety information was obtained, will be analyzed in this investigation. The necessity of switching to a patient registration system that does not require the completion of case report forms (CRFs) will be judged in consultation with the Pharmaceuticals and

Medical Devices Agency, after confirming that the target information can be collected based on the registration status, CRF collection status, and other information before the number of patients registered reaches the planned sample size.

3. Study Population

All patients who received Arzerra.

4. Planned Number of Study Sites by Department

All the institutions where Arzerra was used (planned to be approximately 200 institutions).

5. Study Method

1) Explanation to planned delivery sites

The person in charge of medical information or monitor (hereinafter referred to as the "person in charge") will provide explanations about the proper product use, safety measures, and cooperation with the drug use investigation to an institution to which Arzerra is planned to be delivered. After obtaining the agreement for cooperation, the person in charge will deliver Arzerra to the institution.

2) Requesting delivery sites to implement the drug use investigation

The person in charge will explain the study objectives, study population, study method, etc. to the delivery site of Arzerra, and request them to cooperate with the investigation.

3) Conclusion of contract

Based on the acceptance of the request for cooperation with this investigation, a contract will be concluded with the delivery site of Arzerra using the designated form of GlaxoSmithKline K.K (Attachment 1) or the form designated by the site.

4) Registration of patients

This investigation will be conducted by an all-patient survey method. The investigator will enter the information of all patients who received Arzerra in the registration form, and promptly register them in the Registration Center (PMS Department, GlaxoSmithKline K.K) by FAX.

<Registration Center>
6-15, Sendagaya 4-chome Shibuya-ku, Tokyo 151-8566 Japan

PMS Department, GlaxoSmithKline K.K
[redacted]

Patients who started receiving Arzerra after marketing but before conclusion of the contract, as well as those who continue to receive Arzerra started at another medical institution or department will also be enrolled in the investigation.

5) Observation period
The standard observation period for each patient is from the start of treatment with Arzerra to 3 months after completion of the treatment (up to 9 months from the start day of treatment with Arzerra).

6) Completion of CRFs
For each patient, the investigator will enter necessary information in the CRF after completion of the observation period, and submit it to the person in charge.

7) All-patient Survey Confirmation Form
The investigator will confirm the registration of all patients who received Arzerra after the end of the study period, and sign or affix his/her name and seal to the "All-patient Survey Confirmation Form", and submit it to the person in charge.

6. Planned Study Period

Study period for 300 patients: Planned to be 5 years (registration period for 300 patients: 4 years and 3 months; observation period: up to 9 months from the start day of treatment with Arzerra)
Registration period: From the day of initial marketing of Arzerra to the day of lifting of the conditions for approval.

7. Study Items

1) Information on institutions and patients
Names of the institution, department, and investigators, identification number, date of birth (or age at the start of treatment), gender, start day of treatment with Arzerra, previous treatment with Arzerra at other institutions
2) Patient characteristics
Hospitalization status, reason for Arzerra use, pregnancy status, appreciable constitutional/hypersensitive predispositions, prior medical history, complications, HBV infection, date of diagnosis of CLL

3) Prior medications
Antineoplastic pharmacotherapy: Presence or absence, drug name, time of discontinuation, route of administration
Hematopoietic stem cell transplantation: Presence or absence, transplantation category, date of transplantation
4) Conditions at the first administration
Disease stage (Rai stage, Binet stage), ECOG PS, chromosomal aberration, number of lines of Arzerra treatment, and prior anti-CD20 antibody therapy at the first administration
5) Conditions at each administration (1st to 12th administrations)
Date, premedication, total dose of Arzerra, infusion rate, etc. of Arzerra, infusion reactions (event name, intervention, onset time, medication status at the time of onset, outcome, outcome date, significance ,seriousness, reason for judging as serious, grade, relationship to Arzerra, factors suspected of being associated with the event other than Arzerra, treatment status of Arzerra after onset of the event)
6) Concomitant medications
Presence or absence, drug name, daily dose, dosage unit, duration of treatment, reason for use
7) Concomitant therapies
Presence or absence, details, reason, duration of therapy
8) Outcome
Date of outcome confirmation, survival/death
9) Discontinuation or completion of treatment with Arzerra
Date of decision, reason
10) Efficacy
Best response
11) Priority study items
Presence or absence
12) Adverse events (AEs)
Presence or absence, AE term, onset date, outcome of AE, outcome date, significance, seriousness, reason for judging as serious, grade, relationship to Arzerra, factors suspected of being associated with AE other than Arzerra, treatment status of Arzerra after onset of AE

8. Analysis Items and Methods

1) Analysis items
(1) Items related to patient disposition

[1] Number of patients registered, number of patients whose CRF was retrieved
[2] Number of patients included in the safety and efficacy analysis sets, number of patients excluded from the analysis sets and reason for exclusion

(2) Items related to safety
[1] Status of occurrence of ADRs and infections (e.g., type, severity and incidence of ADRs, etc.)
[2] Factors that may affect safety (e.g., type and incidence of ADRs, etc. by patient characteristics)
[3] AEs that occurred during or after treatment with Arzerra (items considered necessary to identify the severity and specific trends and to assess the relationship to Arzerra)

(3) Items related to efficacy
Factors that may affect efficacy

(4) Priority study items
Status of occurrence of infusion reactions, infections, tumour lysis syndrome, hematotoxicity, intestinal obstruction, skin disorder, cardiac disorder, blood pressure decreased, hepatic dysfunction/jaundice, renal disorder, and interstitial lung disease

2) Analysis methods
Statistical analyses will be performed for the above items related to safety and efficacy, using Wilcoxon one-sample test, Fisher's exact test, χ^2test, etc. according to need.

9. Study Organization

As described in the Attachment to the basic plan for post-marketing surveillance.
Person responsible for the investigation: [redacted] Manager, Planning Group, PMS Department

10. Name and Address of the Contractor, and the Scope of Outsourced Operations

1) Contractor
Undecided.

2) Scope of outsourced operations
Undecided.

11. Other Necessary Matters

1) Protocol amendments

During the study period, the progress of the investigation, number of dropouts, occurrence of unknown/serious ADRs, a significant increase in the incidence of specific ADRs, appropriateness of study items, etc. should be assessed at all times, and the study protocol should be reviewed and revised if necessary.
In case of making changes to the protocol for the drug use investigation, a change notification should be submitted to the Ministry of Health, Labour and Welfare in advance, except for minor changes.

<Examples of minor changes>

(1) Change of the planned number of study sites (by department)
(2) CRF
    [1] Modifications to the layout of the CRF (relocation of items, enlargement or reduction of sections)
    [2] Change in the explanation of items
    [3] Inclusion of additional examples of ADRs, in association with a revision of the Precautions or inclusion of noteworthy ADRs
(3) Study items
    Addition, change, and deletion of items that have no impact on the entire investigation, particularly efficacy and safety analyses
(4) Study period
    [1] Change of the start day of the investigation due to a delay in the product launch
    [2] Prolongation of the study period to correspond to a short-term (within 3 months) prolongation, if necessary, of the registration period
    [3] Shortening of the study period in the absence of changes in the planned sample size

2) Handling of problems or questions detected
If any problem is found during the study period or in the evaluation and analysis results, etc. after completion of the investigation, implementation of a special drug use investigation or post-marketing clinical study will be considered according to need.

3) Interim analysis
An interim analysis will be performed when the number of patients with finalized CRFs reaches 100 or after 3 years from the start of the investigation, whichever comes earlier. Information obtained from the analysis will be provided to the medical front.

4) Definition of infusion reactions

Infusion reactions are defined as events that occurred after the start of infusion on the day of infusion of Arzerra and that led to temporary infusion interruption, prolongation of the infusion time, or discontinuation of infusion. The signs/symptoms of infusion reactions that occurred after the start of intravenous drip infusion of Arzerra are listed in the table below. These signs /symptoms of infusion reactions should be those that have been confirmed as clinical signs/symptoms characteristic of the infusion reactions to anti-CD20 antibodies, based on the package inserts of other monoclonal antibodies.

Table Signs/symptoms regarded as infusion reactions

Category	Event name
Anaphylaxis-related events	Anaphylactic reaction, anaphylactoid reaction, cytokine release syndrome, drug hypersensitivity, hypersensitivity
Arrhythmia	Bradycardia, palpitations, sinus tachycardia, supraventricular extrasystoles, tachycardia, ventricular extrasystoles
Cardiac events	Acute coronary syndrome, angina pectoris, atrial flutter, bradycardia, arrhythmia, cardio-respiratory arrest, microvascular angina, myocardial infarction, myocardial ischemia, palpitations, sinus tachycardia, supraventricular extrasystoles, tachycardia, paroxysmal tachycardia, ventricular dysfunction, ventricular extrasystoles
Chills	Chills
Cough	Cough, productive cough
Diarrhea	Diarrhea, infectious diarrhea
Dry mouth	Dry mouth, dry throat, throat irritation
Dyspnea	Dyspnea, exertional dyspnea
Pyrexia	Pyrexia, hyperthermia
Flushing	Feeling hot, flushing
Headache	Headache, sinus headache
Hyperhidrosis	Hyperhidrosis
Hypertension	Blood pressure increased, hypertension
Hypotension	Hypotension, orthostatic hypotension
Edema	Face edema, generalized edema, localized edema, edema, mucosal edema, peripheral edema, pitting edema
Pain	Lower abdominal pain, back pain, bone pain, gastrointestinal pain, musculoskeletal chest pain, musculoskeletal pain, esophageal pain, oral pain, oropharyngeal pain, pain, pain in extremity, pain in jaw, pain of skin, proctalgia, non-cardiac chest pain
Pruritus	Pruritus, generalized pruritus
Rash	Rash, generalized rash, macular rash, pruritic rash, pustular rash
Sinusitis	Sinusitis
Skin discolouration	Skin discolouration
Syncope	Syncope, vagovagal syncope
Urticaria	Urticaria
Vomiting	Vomiting

12. Attachments

Attachment 1 Contract for the Drug Use Investigation

Attachment 2 Implementation Guidance for the Drug Use Investigation

Attachment 3 Registration Form for the Drug Use Investigation

Attachment 4 Case Report Form for the Drug Use Investigation

Attachment 5 Case Report Form for Use During Pregnancy

Attachment 6 Case Report Form: Report Form for Serious Adverse Events

Created on 28 March 2013 (Version 1)