Clinical Study Protocol

NCT Number: NCT02415712

Title: Drug Use Surveillance of Fomepizole Intravenous Infusion "Takeda" (All-Case Surveillance)

Study Number: Fomepizole-5001

Document Version and Date: Version 6 / 27-Sep-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

Note; This document was translated into English as the language on original version was Japanese.

DRUG USE SURVEILLANCE PROTOCOL

Drug Use Surveillance of Fomepizole Intravenous Infusion "Takeda"

(All-Case Surveillance)

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol Number	**Fomepizole- 5001**
Version Number	**Version 6**
Prepared on	**27 September 2022**

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1.0 BACKGROUND

To date, there have been no clinical studies of fomepizole intravenous infusion (brand name: "Takeda"; herein "fomepizole IV") in Japan,
and there are virtually no reports in the literature or elsewhere on the use of fomepizole IV in Japanese individuals. As such, there is a need to evaluate the safety and efficacy of fomepizole IV used by Japanese individuals in clinical practice.
The Drug Use Surveillance described in this Protocol (herein "the Surveillance" or "the DUS") was therefore planned to evaluate the safety and efficacy of fomepizole IV when used in clinical practice to treat patients with ethylene glycol and methanol poisoning. The DUS will be conducted in compliance with Japan's Ministerial Ordinance on Good Postmarketing Study Practice (GPSP) and other relevant regulatory requirements.

2.0 OBJECTIVES

To evaluate the safety and efficacy of fomepizole IV when used in clinical practice to treat Japanese patients with ethylene glycol and methanol poisoning.

3.0 PLANNED SAMPLE SIZE AND RATIONALE

3.1 Planned Sample Size

All patients confirmed to have received fomepizole IV during the 7 years since it was first marketed in Japan

3.2 Rationale

The planned sample size was selected to enable the submission of DUS results within the specified period following the end of the reexamination period.

4.0 SURVEILLANCE POPULATION

The DUS will target all patients confirmed to have received fomepizole IV.

5.0 DOSAGE AND ADMINISTRATION

The standard dosage will consist of an initial dose of 15 mg/kg, second through fifth doses of 10 mg/kg, and sixth and subsequent doses of 15 mg/kg fomepizole IV to be administered every 12 hours by IV infusion over a period of at least 30 minutes.
When administered in combination with hemodialysis, fomepizole IV will be given as follows.

At start of dialysis	If less than 6 hours have elapsed since the previous infusion, do not administer fomepizole IV immediately before starting dialysis.
	If 6 or more hours have elapsed since the previous infusion, administer fomepizole IV immediately before starting dialysis.
During dialysis	Administer fomepizole IV every 4 hours after starting dialysis.

At end of dialysis	If less than 1 hour has elapsed since the previous infusion, do not administer fomepizole IV at the end of dialysis.
	If between 1 and 3 hours have elapsed since the previous infusion, administer fomepizole IV at 50% of the standard dose at the end of dialysis.
	If more than 3 hours have elapsed since the previous infusion, administer fomepizole IV immediately after the end of dialysis.
After end of dialysis	Administer fomepizole IV every 12 hours after the previous infusion.

6.0 PLANNED NUMBER OF SURVEILLANCE SITES BY DEPARTMENT

All sites where fomepizole IV is administered

7.0 METHODS

7.1 Observation Period

From the start of treatment with fomepizole IV until hospital discharge (or until transfer to another department)

7.2 Patient Enrollment Method

Patients will be enrolled retrospectively using a central enrollment procedure and transmitted via fax. Specifically, the surveillance site investigator (herein "the investigator") will fill out the enrollment details of patients treated with fomepizole IV on the "Contact Form" enclosed in the drug product packaging (see section 9.1) and will then send the completed form by fax to the Central Enrollment Center (see section 12.3).

7.3 Surveillance Site Recruitment and Contracting

The DUS will be conducted using paper-based Case Report Forms (CRFs). A representative of Takeda Pharmaceutical Company Limited (herein "Takeda representative") will contact medical institutions where fomepizole IV has definitely or potentially been administered, and will explain the objectives and details of the DUS using the "Request to Participate in Drug Use Surveillance," "Outline of the Drug Use Surveillance" and "Sample Case Report Form." The medical institutions that agree to participate in the DUS (i.e., the surveillance sites) will sign a written agreement, and the investigators will be requested to perform the required surveillance tasks within the specified surveillance period.

7.4 Completion and Submission of Case Report Forms

The investigators will fill out a CRF for each enrolled patient and will submit the completed CRFs to Takeda Pharmaceutical within approximately 1 month of the end of the observation period.

7.5 Actions To Be Taken In Response To Serious Adverse Events

If a serious adverse event (SAE) occurs, the investigator will immediately notify the Takeda representative. The investigator will also provide additional details of the SAE if requested by the Takeda representative.

8.0 PLANNED DURATION OF SURVEILLANCE

Surveillance period: From the start of fomepizole IV marketing in Japan until 30 June 2022

Patient enrollment period: From the start of fomepizole IV marketing in Japan until 31 January 2022[N.B.)]

[N.B.)] Patients will not be enrolled (i.e., Contact Forms sent via fax will not be accepted) from 1 February 2022 onwards even if they had received fomepizole IV on or before 31 January 2022.

9.0 SURVEILLANCE DATA ELEMENTS

The investigator will fill out the following surveillance information (herein "data elements") on the Contact Form and CRF. The DUS schedule is presented in the Appendix.

9.1 Contact Form Data Elements

1) Surveillance data elements

Name of surveillance site, name of investigator filling out the Contact Form, contact details, reason for using fomepizole IV, start date of fomepizole IV treatment, patient identification (ID) number, patient initials, sex, age (at start of fomepizole IV treatment)

2) Surveillance timing

At patient enrollment

9.2 Case Report Form Data Elements

9.2.1 Case Report Form Cover Sheet

Date of last CRF entry, name of investigator filling out the CRF

9.2.2 Patient Demographics and Baseline Characteristics

1) Surveillance data elements

Diagnosis, hypersensitivity factors (Y/N, details), concurrent (coexisting) disease*[1] (Y/N, details), previous medical history (Y/N, details), height, body weight, alcohol consumption (Y/N; at time of poisoning), pregnancy (Y/N; females only)*[2], level of consciousness, circumstances of poisoning (ingested substance and amount, time and date ingested, route of ingestion, reason ingested)

*[1] Disease/s the patient has at the start of fomepizole IV treatment

*[2] The Takeda representative must be notified immediately if a patient is found to be pregnant. Pursuant to a request by the Takeda representative, the investigator will submit detailed information on the pregnancy using the Pregnancy Form (including, where feasible, details on the outcome of the pregnancy such as premature delivery).

2) Surveillance timing

At the start of treatment with fomepizole IV
However, the diagnosis should be recorded in the CRF during the observation period.

9.2.3 Treatment Details

1) Surveillance data elements

Administration of fomepizole IV (number of infusions, dose per infusion, infusion dose per body weight, treatment duration, and reason for discontinuing fomepizole IV treatment), interventions/procedures (other than pharmacotherapy) (Y/N, details), administration of medications (other than fomepizole IV) (Y/N, drug name/s and reason/s for use)

2) Surveillance timing

The period from the start to the end of treatment with fomepizole IV (herein "fomepizole IV treatment period")

However, surveillance of the data elements 'interventions/procedures (other than pharmacotherapy)' and 'administration of medications (other than fomepizole IV)' will be performed from the time of poisoning until completion of the final fomepizole IV infusion.

9.2.4 Tests and Observations

9.2.4.1 Vital Signs

1) Tests and observations

Pulse rate, blood pressure (systolic/diastolic), respiratory rate, body temperature

2) Surveillance timing

Test timepoints at the start of fomepizole IV dosing, 0.5 hr post-infusion, 4 hr post-infusion, 8 hr post-infusion, 12 hr post-infusion, 16 hr post-infusion, 20 hr post-infusion, 24 hr post-infusion, every 12 hours from >24 hr post-infusion, at completion of final infusion, 12 hr after completion of final infusion, 24 hr after completion of final infusion

9.2.4.2 Laboratory Tests

1) Tests

RBC count, WBC count, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (gamma-GTP), serum creatinine, BUN

2) Surveillance timing

Test timepoints at the start of fomepizole IV dosing, 0.5 hr post-infusion, 4 hr post-infusion, 8 hr post-infusion, 12 hr post-infusion, 16 hr post-infusion, 20 hr post-infusion, 24 hr post-infusion, every 12 hours from >24 hr post-infusion, at completion of final infusion, 12 hr after completion of final infusion, 24 hr after completion of final infusion

9.2.4.3 Poisoning/Toxicity Tests

1) Tests and observations

- Arterial blood gas analyses
  Arterial blood pH, arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2)
  , bicarbonate ion, base excess (BE)
- Anion gap
- Blood ethylene glycol concentration
- Blood glycolic acid concentration
- Blood methanol concentration
- Blood formic acid concentration
- Osmotic pressure gap

2) Surveillance timing

Test timepoints at the start of fomepizole IV dosing, 0.5 hr post-infusion, 4 hr post-infusion, 8 hr post-infusion, 12 hr post-infusion, 16 hr post-infusion, 20 hr post-infusion, 24 hr post-infusion, every 12 hours from >24 hr post-infusion, at completion of final infusion, 12 hr after completion of final infusion, 24 hr after completion of final infusion

9.2.4.4 Toxic Symptoms

1) Observations

Presence or absence (Y/N) of toxic symptoms

2) Surveillance timing

At the start and at the end of treatment with fomepizole IV

9.2.4.5 Outcomes

1) Observations

Outcome and sequelae details

2) Surveillance timing

At hospital discharge (or transfer to another department)

9.2.5 Adverse Events

1) Surveillance data elements

Presence or absence (Y/N) of adverse event (herein "AE"; see Table 1), AE term, date of onset, seriousness and reason for assessment as serious (see Table 2), reason for discontinuing fomepizole IV, date of outcome assessment, outcome, causal relationship with fomepizole IV* (see Table 3)

If the AE outcome is "not recovered/not resolved" or "unknown" or the causal relationship is deemed "not evaluable," the patient should be followed to the extent possible.

* If the causal relationship with fomepizole IV is deemed 'not related,' the investigator shall record the

rationale for this assessment. Alternatively, if the causal relationship is deemed 'not evaluable,' the investigator shall provide the reason for this assessment.

N.B.) Points to consider when assessing AEs:

Although abnormal worsening of the target disease (e.g., worsening beyond the expected natural course of the disease) should be assessed as an AE, any expected worsening of the target disease should not be assessed as an AE.

2) Surveillance timing

The period from the start of fomepizole IV dosing until 24 hours after completion of the final infusion

Table 1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product during the course of a clinical investigation, and that does not necessarily have a clear causal relationship with this pharmaceutical product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. The following events are also handled as AEs: · Signs and symptoms appearing in breastfed infants of female patients receiving the pharmaceutical product · Signs and symptoms appearing in children receiving the pharmaceutical product · Signs and symptoms appearing as a result of occupational exposure to the pharmaceutical product · Signs and symptoms appearing after administration of a counterfeit of a pharmaceutical product manufactured and marketed by Takeda Pharmaceutical

Table 2 Criteria for Assessing Seriousness

AEs that meet any of the following criteria will be assessed as serious:

1. Results in death (death)
2. Is life-threatening (risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Leads to a congenital anomaly/birth defect (congenital anomaly)
6. Is an important medical condition according to items 1 to 5 above. This includes events corresponding to those listed in the "Takeda Medically Significant AE List."

Table 3 Criteria for Assessing Causal Relationship of Adverse Events to Fomepizole IV

Assessment	Assessment Criteria
Related	There is a temporal relationship between the onset of the event and administration of fomepizole IV (including the post-treatment course of the event), or it is plausible that the event was caused by the drug despite the possible involvement of other factors such as the underlying disease, concurrent disease or concomitant medication or procedures.
Not related	There is no temporal relationship with the drug, or there is sufficient evidence to suggest that the event was caused by other factors such as the underlying disease, concurrent disease or concomitant medication or procedures.
Not evaluable	There is insufficient information on the temporal relationship (including the post-treatment course of the event), underlying disease, concurrent disease or concomitant medication or procedures to evaluate the causal relationship.

10.0 ANALYSES AND METHODS

10.1 Patient Disposition

Patient disposition will be tabulated for the number of enrolled patients, the number of patients with submitted CRFs, and the respective numbers of patients in the Safety Analysis Set and Efficacy Analysis Set.

10.2 Patient Demographics and Baseline Characteristics

Demographics and baseline characteristics will be tabulated for sex, age, concurrent disease, circumstances of poisoning and other relevant variables.

10.3 Treatment Details

Treatment data will be tabulated for administration of fomepizole IV treatment,

interventions/procedures (other than pharmacotherapy), administration of medications (i.e., drugs other than fomepizole IV) and other relevant variables.

10.4 Safety

The following data will be tabulated in the Safety Analysis Set. AEs will be summarized by Preferred Term (PT) and System Organ Class (SOC) using the Japanese translation of Medical Dictionary for Regulatory Activities (MedDRA/J).

10.4.1 Adverse Event Incidence Data

AE incidences will be tabulated by category, time of onset, seriousness, causal relationship with fomepizole IV and other relevant variables.

10.4.2 Factors Potentially Affecting Safety

AE incidences will be tabulated by patient demographics and baseline characteristics (e.g., sex, age, alcohol consumption [Y/N]), treatment details (administration of fomepizole IV, interventions/procedures [other than pharmacotherapy], administration of medications [other than fomepizole IV]) and presence/absence (Y/N) of toxic symptoms.

10.5 Efficacy

The following data will be tabulated in the Efficacy Analysis Set.

10.5.1 Time Course of Arterial Blood pH

Summary statistics will be calculated for arterial blood pH test values and for absolute change from baseline at each assessment timepoint (i.e., the test value at each assessment timepoint after the start of fomepizole IV dosing minus the baseline test value at the start of fomepizole IV dosing).

10.5.2 Time Course of Poisoning/Toxicity Test Parameters

Summary statistics will be calculated for each poisoning/toxicity test value at each assessment timepoint; specifically $PaCO_2$, PaO_2, bicarbonate ion, BE, anion gap, blood ethylene glycol concentration, blood glycolic acid concentration, blood methanol concentration, blood formic acid concentration and osmotic pressure gap.

10.5.3 Time Course of Toxic Symptoms

The numbers of patients with and without toxic symptoms at the start of fomepizole IV treatment (i.e., at baseline) and at completion of the final fomepizole IV infusion and the proportions of these patient subsets relative to the Efficacy Analysis Set will be tabulated. Presence or absence of toxic symptoms at baseline will also be cross-tabulated against those at completion of the final fomepizole IV infusion.

10.5.4 Outcomes

The numbers of patients with each outcome at hospital discharge (or at transfer to another department) and the proportions of these patient subsets relative to the Efficacy Analysis

Set will be calculated, and the details of any sequelae will be described.

10.5.5 Factors Potentially Affecting Efficacy

Summary statistics for time course of arterial blood pH will be calculated by patient demographics and baseline characteristics (e.g., sex, age, alcohol consumption [Y/N]), treatment details (administration of fomepizole IV, interventions/procedures [other than pharmacotherapy], administration of medication [other than fomepizole IV]) and presence/absence (Y/N) of toxic symptoms.

11.0 REGISTRATION OF SURVEILLANCE INFORMATION

Takeda Pharmaceutical Company Limited will register information about this DUS on the following publicly-accessible websites prior to commencing the surveillance.

- Japic Clinical Trials Information website, Japan Pharmaceutical Information Center (JAPIC): Japan Pharmaceutical Information Center-Clinical Trials Information
- ClinicalTrials.gov clinical trials registry, U.S. National Institutes of Health (NIH): ClinicalTrials.gov

12.0 SURVEILLANCE ADMINISTRATIVE STRUCTURE

12.1 Administrative Structure for Postmarketing Surveillance and Other Related Tasks

See the attached document.

13.0 MEDICAL ADVISOR

Advises on the preparation and revision of the Protocol and other documents pertaining to this DUS.

Also advises on various medical decisions pertaining to the conduct of this DUS.

[redacted]

14.0 CENTRAL ENROLLMENT CENTER

EPS Corporation

[redacted]

15.0 CONTRACT RESEARCH ORGANIZATIONS

(1) PRA Health Sciences Co., Ltd.
Address: 4-1-3 Kyutaro-machi , Chuo-ku, Osaka City
Contracted operations: Data management operations, archiving and storage of records, postmarketing surveillance support operations

(2) EPS Corporation
Address: 2-23 Shimomiyabi-cho, Shinjuku-ku, Tokyo
Contracted operations: Data management operations, statistical analyses, medical writing

(3) PharField Corporation

Address: 2-8-20 Saga, Koto-ku, Tokyo
Contracted operations: Monitoring operations

(4) WysiWyg Co., Ltd.
Address: 2-21-2 Hatchobori, Chuo-ku, Tokyo
Contracted operations: Medical writing

16.0 OTHER NECESSARY INFORMATION

16.1 Protocol Amendments

The DUS Protocol will be revised and amended during the surveillance period where necessary based on information obtained in relation to the study progress, the onset of ADRs or serious ADRs that were not expected based on the PRECAUTIONS section of the Japanese Package Insert, any increases in the frequency of known ADRs, and the appropriateness of the surveillance data elements, etc. The Protocol will also be amended as required during the surveillance period where deemed necessary in response to a partial change in the approved Dosage and Administration and/or Indications specified in the marketing authorization, etc.

16.2 Handling of Any Issues or Uncertainties

If any safety or efficacy issues are identified, measures to address these issues shall be investigated based on careful scrutiny of the available data.

Appendix Schedule of Assessments (1)

Surveillance data elements \ Surveillance timing		Observation timepoint												
		At patient enrollment	At start of fomepizole IV dosing	0.5 hr post infusion	4 hr post-infusion	8 hr post-infusion	12 hr post-infusion	16 hr post-infusion	20 hr post-infusion	24 hr post-infusion	Every 12 hr from >24 hr post-infusion	At completion of final infusion	12 hr after completion of final infusion	24 hr after completion of final infusion	At hospital discharge
Patient enrollment	Reason for using fomepizole IV	o													
	Start date of fomepizole IV treatment	o													
	Patient ID No.	o													
	Patient initials	o													
	Sex	o													
	Age (at start of fomepizole IV treatment)	o													
Patient demographics & baseline characteristics	Diagnosis*		o												
	Hypersensitivity factors		o												
	Concurrent (coexisting) disease		o												
	Previous medical history		o												
	Height		o												
	Body weight		o												
	Alcohol consumption (Y/N; at time of poisoning)		o												
	Pregnancy (Y/N; females only)		o												
	Level of consciousness		o												
	Circumstances of poisoning		o												
Treatment details	Administration of fomepizole IV		←	―	―	―	o	―	―	―	―	→			
	Interventions/procedures (other than pharmacotherapy)**		←	―	―	―	o	―	―	―	―	→			
	Administration of medications (other than fomepizole IV)**		←	―	―	―	o	―	―	―	―	→			
Tests, observations & other assessments	Pulse rate		o	o	o	o	o	o	o	o	o	o	o	o	
	Blood pressure (systolic/diastolic)		o	o	o	o	o	o	o	o	o	o	o	o	
	Respiratory rate		o	o	o	o	o	o	o	o	o	o	o	o	
	Body temperature		o	o	o	o	o	o	o	o	o	o	o	o	
	RBC count		o	o	o	o	o	o	o	o	o	o	o	o	
	WBC count		o	o	o	o	o	o	o	o	o	o	o	o	
	Platelet count		o	o	o	o	o	o	o	o	o	o	o	o	
	AST		o	o	o	o	o	o	o	o	o	o	o	o	
	ALT		o	o	o	o	o	o	o	o	o	o	o	o	
	Gamma-GTP		o	o	o	o	o	o	o	o	o	o	o	o	
	Serum creatinine		o	o	o	o	o	o	o	o	o	o	o	o	
	BUN		o	o	o	o	o	o	o	o	o	o	o	o	

o : Performed

←o→ : Performed throughout the observation period.

*: Performed during the observation period based on assessment of test/observation findings and toxic symptoms.

**: Surveyed from the onset of poisoning.

Appendix Schedule of Assessments (2)

Surveillance data elements \ Surveillance timing		Observation timepoint												
		At patient enrollment	At start of fomepizole IV dosing	0.5 hr post-infusion	4 hr post-infusion	8 hr post-infusion	12 hr post-infusion	16 hr post-infusion	20 hr post-infusion	24 hr post-infusion	Every 12 hr from >24 hr post-infusion	At completion of final infusion	12 hr after completion of final infusion	24 hr after completion of final infusion	At hospital discharge
Tests, observations & other assessments	Arterial blood pH		o	o	o	o	o	o	o	o	o	o	o	o	
	$PaCO_2$		o	o	o	o	o	o	o	o	o	o	o	o	
	PaO_2		o	o	o	o	o	o	o	o	o	o	o	o	
	Bicarbonate ion		o	o	o	o	o	o	o	o	o	o	o	o	
	BE		o	o	o	o	o	o	o	o	o	o	o	o	
	Anion gap		o	o	o	o	o	o	o	o	o	o	o	o	
	Blood ethylene glycol concentration		o	o	o	o	o	o	o	o	o	o	o	o	
	Blood glycolic acid concentration		o	o	o	o	o	o	o	o	o	o	o	o	
	Blood methanol concentration		o	o	o	o	o	o	o	o	o	o	o	o	
	Blood formic acid concentration		o	o	o	o	o	o	o	o	o	o	o	o	
	Osmotic pressure gap		o	o	o	o	o	o	o	o	o	o	o	o	
	Toxic Symptoms		o									o			
	Outcomes														o
	Adverse Events		←o→												

o : Performed

←o→ : Performed throughout the observation period

Document History

Version	Date	Comments
original version	2014/12/22	New document
2nd version	2015/4/1	Additions and clarifications concerning the contracted operations of CROs
3rd version	2017/6/2	Clarifications and changes & additions to the CROs
4th version	2021/1/26	Clarifications and changes & additions to the CROs
5th version	2022/4/28	The appended Administrative Structure for Postmarketing Surveillance Operations chart
6th version	2022/9/27	Changes & additions to the CROs and additions to the CRO contracted operations