Title: RIXUBIS Drug Use-Result Survey (Japan)

NCT Number: NCT02937831

Protocol Approve Date: 01-Oct-2020

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

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

DRUG USE-RESULT SURVEY

PRODUCT: RIXUBIS

PROTOCOL IDENTIFIER: 251601

VERSION 4.0: 2020 Oct 01

MARKETING AUTHORISATION HOLDER	**Takeda Pharmaceutical Company Limited** 4-1-1 Dosho-machi Chuo-ku, Osaka Japan

SUMMARY OF CHANGES

Protocol Amendments		
Summary of Change(s) since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **01 Oct 2020**	
Description of Change		**Section(s) Affected by Change**
MAH for RIXUBIS changed from Shire Japan KK to Takeda Pharmaceutical Company Limited		Cover page 1
Address changed to Takeda Pharmaceutical Company Limited 4-1-1 Dosho-machi Chuo-ku, Osaka Japan		Cover page 1
Version number changed		Cover page 1
Delete outsourcing		Section 3.9 Outsource Details

See Appendix 2 for protocol history, including all amendments

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Tables

1. PURPOSE

This survey will be conducted to understand the following items observed in the actual clinical use of RIXUBIS in patients.

1. Unexpected adverse drug reactions
2. Occurrence of adverse drug reactions in the actual clinical use
3. Factors that may affect safety and effectiveness
4. Occurrence of Factor IX inhibitor development in patients with coagulation factor IX deficiency (hereinafter hemophilia B)
5. Safety and effectiveness for hemophilia B patients who received routine prophylactic therapy, on-demand therapy and perioperative therapy

2. SAFETY SPECIFICATION

1. Inhibitor development (Factor IX inhibitor)
2. Shock, anaphylaxis
3. Thromboembolism

3. PROTOCOL

3.1 Estimated number of patients in the survey and the rational

Estimated number of subjects for the survey: 30

Rational: There are currently about 250 hemophilia B patients who receive recombinant formulation of Factor IX in Japan. The expectation of the number of patients switching from current products to RIXUBIS is supposed to be limited while other new products are under development, resulting in the determining of the collectible subject number of 30. Of note, the number is considered enough to retain 95% reliability for detecting unexpected adverse reactions with incidence of 10%.

3.2 Targeted patients

All patients with hemophilia B receiving RIXUBIS after its launching at medical institutions which contracted this investigation.

Indications: Suppression of bleeding tendency in patients with factor IX deficiency.

Administration method and dosage: RIXUBIS is reconstituted with the attached 5 mL reconstitution diluent and administered by intravenous injection. Do not infuse any faster than 10 mL per minute. Normally, administer 50 international units per kg body weight per time. Adjust a dose based on a patient's condition.

For routine dosing, normally administer 40-75 international units per kg body weight twice a week. For pediatric subjects under the age of 12 years, administer 40-80 international units per kg body weight twice a week.

3.3 Estimated number of centers (departments)

Thirty departments (or centers) are expected to be involved nationwide, including pediatrics department, internal medicine (hematology) department and others.

3.4 Survey Method

This survey is conducted using paper-based case report forms (CRFs). The procedure is as follows.

1. Request and contract of the survey
   Medical representatives in the Company request medical institutions to conduct the surveillance in writing after confirming the list below and conclude a contract.
   - There are physicians with experience in hemophilia therapy in the medical institution
   - RIXUBIS is planned to be used for patients who are targeted in this surveillance in the medical institution.
     Upon agreement of implementation of the drug use surveillance, the MAH will enter into agreement with the medical institution using a designated contract document.
2. Registration of patient
   The central registration procedure will be used.
   The investigator registers all patients receiving RIXUBIS after its launching at medical institutions(in principle).
   The investigator will complete the required information for registration on case registration forms (site name, medical department name, physician’s name, site management patient number, sex, date of birth, starting date of administration, EDs of other factor IX products before RIXUBIS administration (0-3, 4-50, 51-150, or >150 days), and send them to registration office for drug use surveillance office.

3. CRF collection and observation period during of the survey.
   The survey is conducted using multiple CRFs in parts with 6-month observation period per CRF. The total observation period per subject is as follows.
   - PTPs [i] (Previously treated patients who had more than 4 previous exposure days to other products): One year after the beginning of RIXUBIS administration
   - PUPs (Previously untreated patients who had 3 or less previous exposure days to other products: Two years or 100 EDs after the beginning of RIXUBIS administration whichever comes first

3.5 Estimated implementation period of the survey

The surveillance period is as follows:

Period of survey: June 2016 - May 2022

Period of registration: June 2016 - May 2021

Of note, if 30 subjects are successfully registered before the end of registration period, registration should be sustained as long as possible until the registration period ends.

3.6 Items for investigation

1. Patient demographics at the start of administration
   Identification number, gender, date of diagnosis (age), date of birth, congenital/acquired disease, family history of hemophilia, body height, body weight, inpatient/outpatient status, race, clinical severity of hemophilia (residual factor IX activity, date of measurement), annualized bleeding rate (ABR)[ii], history of factor IX inhibitor measurement (date, value and result of measurement, date and value of peak inhibitor record), family history of inhibitor development, past history of serious bleeding episode (date, hemorrhage intracranial, gastrointestinal hemorrhage, bleeding into the iliopsoas muscle and others), past surgical history (surgery name, surgery date), other past history, hemophilic arthropathy, target joint, complication (including renal and hepatic complications), allergy, previous administration of other factor IX products (product name, EDs, regimens (prophylaxis, on-demand, prophylaxis/on-demand)

2. Concomitant drugs and concomitant therapies

[i] Includes MTPs - Minimally treated patients (>3 exposure days and less than 150 exposure days (Adults) and >3 exposure days and less than 50 exposure days (Pediatrics))

[ii] Patient diary and medical records will be used for the calculation of ABR.

3. Administration status of RIXUBIS
In terms of the treatment during surveillance period of RIXUBIS, administration status and number of bleeding events will be investigated for regular replacement (prophylaxis) therapy, on-demand replacement therapy, and perioperative therapy.

Prophylaxis therapy:
administration period for prophylaxis, frequency of administration, body weight and date of measurement, dosage, total number of doses, number of doses to treat a bleed, number[iii] of bleeding events will be collected.

Purpose of prophylaxis:

- Long-term prophylaxis: Therapy for the purpose of long term (at least 6 months of duration) prevention of bleeding with dosing interval of more than once a week. Less than 2 weeks of untreated periods may be allowed during 6 months.
- Short-term prophylaxis: Therapy for the purpose of relatively short term (less than 6 months of duration) prevention of bleeding with dosing interval of more than once a week.
- Preventive treatment: dosing before events; sports, physical activities, rehabilitations, etc. that may cause bleeding.

On-demand replacement therapy:
Administration period for on-demand, body weight and date of measurement, dosage, number of doses to treat a bleed, number of bleeding events.

Perioperative therapy:
Surgery (minor/major, operative method, date, diagnosis), administration period, body weight and date of measurement, loading dose, subsequent doses during procedure total number of doses, blood transfusion (product type, volume), total number of units, method of administration (administration rate, administration interval).

4. Factor IX inhibitor titer
Date of measurement, measured value, measurement method and others as well as inhibitor development during the surveillance period are investigated routinely.

5. Discontinuations/withdrawals
The timing and reasons for discontinuation/withdrawal will be investigated, if any.

[iii] To enable the calculation of ABR, please record information about bleeding in a patient's diary, etc . if breakthrough bleeding occurs during the prophylaxis therapy.

6. Effectiveness of RIXUBIS
   The effectiveness of RIXUBIS is assessed every six months for regular replacement therapy and on-demand replacement therapy, respectively. Outcome measures are shown in the Appendix.

7. Laboratory tests
   Review values which were voluntarily measured in any medical institution before the start of, and during RIXUBIS administration. In addition, review clinically significant abnormal fluctuation of the laboratory values that were measured in any medical institution at the end of any 6-month observation period or at the time of discontinuation/withdrawal during the maximum 2-year of a total observation period, if any.

8. Adverse events
   Adverse event name, onset date, seriousness, severity, presence of treatment, treatment details, outcome, outcome date, causal relationship to RIXUBIS, presence of autopsy in death case.
   - Inhibitor to RIXUBIS
     - Date(s) of inhibitor detection
     - Date(s) of inhibitor disappearance
     - FIX inhibitor titer(s)
   - Other serious adverse events
     - Event
     - Onset Date
     - Stop Date
     - Severity
     - Disease progression
     - Outcome
     - Action Taken
     - Date of death (if applicable)
     - Cause of death (if applicable)
     - Causality assessment by Investigator
   - Incidence of non-serious adverse events coincident with use of RIXUBIS
     - Event/Type
     - Onset Date
     - Stop Date

- Severity
- Progression
- Outcome
- Action Taken

- Causality assessment by Investigator

9. Additional investigation items at the onset of adverse events

   Upon the occurrence of inhibitor development, shock, anaphylaxis, thromboembolism and others or in the event of adverse drug reactions for which causal relationship to RIXUBIS cannot be denied, additional investigation will be conducted for the following items:

   Lot number of RIXUBIS, administration rate of RIXUBIS, status of concomitant drugs administration (concomitant drug name, whether suspected drug or not, administration route, dosage form, dose, number of doses per day, administration period, reason for use), concomitant therapies, re-administration of suspected drugs, clinical course of the case, etc., laboratory tests (if performed, including abnormal values with clinical significance)

3.7 Statistical Analysis and Analysis Method

1. Analysis items

   a. Subject population
      Number of registered subjects, number of subjects whose CRFs are collected, number of subjects in safety analysis set, number of subjects in the effectiveness analysis set, number of withdrawal/discontinuation, reasons for and details of withdrawal/discontinuation, and others

   b. Items related to Safety
      All patients, PTP/PUP

   c. Hemostatic efficacy
      - Prophylaxis: ABR
      - On-demand: hemostatic effectiveness, number of doses to treat a bleed
      - Surgery: In- and post-surgery hemostatic effectiveness

   Physician rated effectiveness (“none”, “moderate”, “good”, or “excellent”)

2. Analysis method

Mainly, frequency tabulation is performed for classified data and summarization based on mean values and standard deviation is for sequential data. The detail is described in Statistics Analysis Plan.

3.8 Organization Structure for Surveillance

Same as described in Risk Management Plan

3.9 Outsource Details

Contractor for the operations

IQVIA Services Japan KK
Keikyu Dai-Ichi Building 4-10-8 Takanawa Minato-ku Tokyo

Scope of the contract

Registration center, progress management, data management, tabulation analysis, and others.

4. ADDITIONAL MEASURES TO BE POSSIBLY TAKEN BASED ON THE RESULTS OF THE SURVEY AND DECISION CRITERIA FOR THE INITIATION

The Risk Management Plan will be reviewed at suitable points in consideration of the following:

- Necessity to modify risk minimization activities for the current safety investigation items
- Necessity to modify the protocol (such as continuation of the surveillance and implementation of additional surveillances), including necessity to add another safety investigation item
- Necessity to develop risk minimization measures for added safety investigation items, if any.

5. MILESTONES FOR THE IMPLEMENTATION STATUS OF THE SURVEY AND THE ASSESSMENT OF THE RESULTS, OR ANTICIPATED TIMING FOR REPORTING TO PMDA AND THE JUSTIFICATION

At the time of preparing regular safety report and applying the re-examination:

For comprehensive consideration on safety information

At the time of conducting interim analysis and preparing the final report

Once information for 30 subjects is collected, an interim analysis will be conducted including comparison with the results of clinical trials. Then, necessity for continuing further CRF collection will be examined, the conclusion of which is to be reported to PMDA by attaching analysis results obtained at the completion of collecting 30-subject information or in other ways.

6. OTHER NECESSARY MATTERS

1. Revision of the protocol
   Necessity for revising the protocol will be examined based on new findings obtained as the surveillance proceeds, and the protocol will be revised as needed.
2. Actions to be taken when issues or questions are raised
   Propose a hypothesis and then examine necessity of implementing specific drug use surveillance to test it, when occurrence of serious unexpected adverse drug reactions is suggested; when a large increase is found in frequency of adverse drug reactions; when any problem is found in terms of effectiveness or safety compared with the period until the approval of RIXUBIS; or, when occurrence of any abnormal adverse drug reactions is suggested.

APPENDIX 1

Outcome Measure of Treatment Response

Outcome is measured based on the following criteria by the physician/ the investigator or patients

Table 1: Hemostatic effectiveness

Excellent	After a single infusion, complete disappearance of pain and objective decrease of bleeding symptom (swelling, tenderness, and increase in range of motion in musculoskeletal bleeding case) were observed. Additional infusion was not required for haemostasis. Of note, additional infusion for haemostasis maintenance has no impact on this assessment.
Good	After a single infusion, there were definitive relief of pain and improvement of bleeding symptom. In some circumstances, more than 1 infusion may be required for complete resolution.
Fair	After a single infusion, there were a probable or slight relief of pain and a mild improvement of bleeding signs. However, more than 1 infusion was required for complete resolution.
Poor	Improvement was not observed or symptom was aggravated.

In case the subject required an additional infusion prior to the resolution of the bleed, effectiveness was to be assessed at 12 ± 1 and 24 ± 1 hours following the subsequent infusion, and/or at resolution of bleed, if prior to the 12 ± 1 or 24 ± 1 hour post-treatment time-point. If a bleed occurred following resolution of the bleed, this was to be considered a “new” bleed and recorded accordingly.

Overall outcome in perioperative therapy

Outcome is measured based on the following criteria by the physician performing the surgery or the investigator in charge of controlling hemostasis:

Table 2: In-surgery hemostatic effectiveness

Excellent	Amount of bleeding is smaller than expected.
Good	Amount of bleeding is within the expected range
Fair	Amount of bleeding is greater than expected, with use of additional concomitant medication
Poor	Hemostasis difficulty.

Table 3: Post-surgery hemostatic effectiveness

Excellent	Sufficient control of hemostasis.
Good	Hemostasis controlled by increased dose
Fair	Hemostasis with the use of additional concomitant medication
Poor	Hemostasis difficulty.

APPENDIX 2: PROTOCOL HISTORY

Document	Date	Comment
Original Protocol/ Version 1.0	20 MAY 2016	Approved
Version 2.0	05 APR 2018	Administrative changes to the protocol
Version 3.0	19 Mar 2019	The extension of survey period and additional outsourcing
Version 4.0	01 Oct 2020	MAH and outsource details change