Review Report

June 29, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Velexbru Tablets 80 mg
Non-proprietary Name	Tirabrutinib Hydrochloride (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	April 7, 2020
Dosage Form/Strength	Tablets, each containing 86.42 mg of Tirabrutinib Hydrochloride (80 mg of Tirabrutinib)
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 447 of 2019 [*31 yaku*], PSEHB/PED Notification No. 1119-1 dated November 19, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with Waldenström's macroglobulinemia and lymphoplasmacytic lymphoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following conditions. Infection, severe skin disorder, bone marrow depression, hypersensitivity, interstitial lung disease, hepatic dysfunction, and hemorrhage are subject to further investigation through post-marketing surveillance.

Indications

○ Recurrent or refractory primary central nervous system lymphoma
○ Waldenström's macroglobulinemia and lymphoplasmacytic lymphoma

(Underline denotes additions.)

Dosage and Administration

The usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition.

(No change)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Because of extremely limited number of cases in Japanese clinical studies, the applicant is required to conduct a drug use-results survey involving all patients treated with the product after its market launch until obtaining data from a certain number of patients, in order to identify the characteristics of patients using the product and to promptly collect safety and efficacy data so as to take necessary measures for the proper use of the product.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

May 18, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Velexbru Tablets 80 mg
Non-proprietary Name	Tirabrutinib Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	April 7, 2020
Dosage Form/Strength	Tablets, each containing 86.42 mg of Tirabrutinib Hydrochloride (80 mg of Tirabrutinib)
Proposed Indications	○ Recurrent or refractory primary central nervous system lymphoma ○ Waldenström's macroglobulinemia and lymphoplasmacytic lymphoma (Underline denotes additions.)
Proposed Dosage and Administration	The usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition. (No change)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Tirabrutinib Hydrochloride (hereinafter referred to as tirabrutinib) is a low molecular weight compound discovered by the applicant, with an inhibitory effect on Bruton's tyrosine kinase (BTK). Tirabrutinib is thought to inhibit B-cell tumor growth by binding to BTK, a downstream signal transduction molecule of B cell receptor (BCR) expressed in B cells.

In Japan, tirabrutinib was approved in March 2020 for the indication of "recurrent or refractory primary central nervous system lymphoma."

1.2 Development history etc.

The applicant began the clinical development of tirabrutinib for the treatment of Waldenström's macroglobulinemia (WM) and lymphoplasmacytic lymphoma (LPL) with a Phase II study (Study ONO-4059-05 [Study 05]) in patients with WM or LPL from November 2018 in Japan.

As of May 2020, tirabrutinib has not been approved with the indication for WM or LPL in any country or region.

Recently, an application for partial changes was submitted for additional indication of WM and LPL with pivotal data from Study 05.

Tirabrutinib was designated as an orphan drug with the intended indication of "Waldenström's macroglobulinemia and lymphoplasmacytic lymphoma" in November 2019 (Orphan Drug Designation No. 447 of 2019 [*31 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication, no new quality-related data were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication, no new non-clinical pharmacology data were submitted. Non-clinical pharmacology data had been reviewed for the initial approval.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication, no new data on non-clinical pharmacokinetics were submitted. The non-clinical pharmacokinetics data had been reviewed for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication, no new toxicity data were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication, no new biopharmaceutic study data or associated analytical methods were submitted. Relevant data had been reviewed for the initial approval.

New clinical pharmacology data were submitted for the present application. PMDA concluded that the applicant's explanation was generally consistent with the data evaluated for the initial approval.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The submitted efficacy and safety evaluation data included results from 2 Japanese Phase I studies, 1 Japanese Phase I/II study, 1 Japanese Phase II study, and 1 foreign Phase I study as listed in Table 1. The table also lists results of 3 foreign Phase I studies as reference data. In this section, the dose of tirabrutinib is expressed in terms of free base.

Table 1. List of clinical studies on efficacy and safety

Data category	Region	Study ID	Phase	Study population	Number of enrollments	Dosage regimen	Main endpoint
Evaluation	Japan	01	I	Patients with recurrent or refractory B-NHL or CLL	17	Oral tirabrutinib 160-480 mg QD or 300 mg BID (fasted)	Safety PK
		04	I	Healthy adults	36 (a) 12 (b) 12 (c) 12	(a) A single oral dose of tirabrutinib 320 mg (fasted or fed) (b) A single oral dose of tirabrutinib 20 mg (fed) with itraconazole (c) Oral tirabrutinib 320 mg QD (fed) for 5 days with midazolam	PK
		02	I/II	Patients with recurrent or refractory PCNSL	44 (a) 20 (b) 7 (c) 17	(a) Oral tirabrutinib 320 mg QD (b) Oral tirabrutinib 480 mg QD (c) Oral tirabrutinib 480 mg QD (fasted)	Efficacy Safety PK
		05	II	Patients with WM or LPL	27	Oral tirabrutinib 480 mg QD (fasted)	Efficacy Safety
	Foreign	POE001	I	Patients with recurrent or refractory B-NHL or CLL	90 (a) 62 (b) 28	(a) B-NHL, Oral tirabrutinib 20-600 mg QD or 240 mg BID (fasted) (b) CLL, Oral tirabrutinib 20-600 mg QD or 300 mg BID (fasted)	Safety PK
Reference	Foreign	1765	I	Healthy adults	15	A single oral dose of tirabrutinib 100 mg (fasted) with rifampicin	PK
		1767	I	Healthy adults	76 (a) 16 (b) 24 (c) 24 (d) 12	(a) A single oral dose of tirabrutinib 100 mg (capsule or tablet) (fasted) (b) A single oral dose of tirabrutinib 100 mg (tablet) or 75 mg (capsule) (fasted or fed) (c) A single oral dose of tirabrutinib 100 mg (tablet) or 75 mg (capsule) (fasted) with omeprazole (d) A single oral dose of tirabrutinib 100 mg (tablet) (fasted or fed)	PK
		1768	I	Healthy adults	8	A single oral dose of tirabrutinib 75 mg (fasted)	PK

The clinical study is summarized below. The data of clinical studies other than Study 05 were submitted with the initial application (see "Review Report of Velexbru Tablets 80 mg, dated February 6, 2020"), the summaries of these studies are thus omitted.

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Japanese Phase II study (CTD 5.3.5.2-1, Study 05 [ongoing since November 2018 (data cut-off [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted in patients with WM or LPL (target sample size, 18 in Cohort A [treatment-naïve WM or LPL] and 8 in Cohort B [recurrent or refractory WM or LPL]) to investigate the efficacy and safety of tirabrutinib at 19 study sites in Japan.

Tirabrutinib 480 mg was administered orally QD under fasted conditions[1)] until discontinuation criteria met.

All of the 27 patients enrolled in the study (18 in Cohort A, 9 in Cohort B) received tirabrutinib and were included in the efficacy and safety analysis population.

Table 2 shows the results of the primary efficacy endpoint, i.e., response rate[2)] according to the centralized assessment based on the International Workshop on Waldenström's Macroglobulinemia (IWWM) Criteria (*Br J Haematol.* 2013;160:171-6) in Cohorts A and B.

Table 2. Best overall response and response rates (centralized assessment, efficacy analysis population, data cut-off [redacted], 20[redacted])

Best overall response	Number of patients (%)	
	Cohort A (treatment-naïve patients) (n = 18)	Cohort B (recurrent or refractory patients) (n = 9)
CR	0	0
VGPR	3 (16.7)	0
PR	13 (72.2)	8 (88.9)
MR	1 (5.6)	1 (11.1)
SD	1 (5.6)	0
PD	0	0
Response (CR, VGPR, or PR)	16	8
(Response rate [95% CI (%)*)	(88.9 [65.3, 98.6])	(88.9 [51.8, 99.7])

*Clopper-Pearson method

In Cohort B, the response rate was 85.7% (6 of 7) in patients with recurrent[3)] WM or LPL and 100% (2 of 2) in patients with refractory[4)] WM or LPL.

No death occurred during the treatment with tirabrutinib or within 28 days after the end of treatment.

1) Tirabrutinib was administered under fasting conditions before breakfast as a rule.
2) The threshold response rate in Cohort A (treatment-naïve WM or LPL) was set at 45.0% by referring to the clinical study data on rituximab (*Leuk Lymphoma.* 2004;45:2047-55), bortezomib (*Clin Cancer Res.* 2007;13:3320-5), and fludarabine (*J Clin Oncol.* 2013;31:301-7). The threshold response rate in Cohort B (recurrent or refractory WM or LPL) was set at 20.0% by referring to the clinical study data on rituximab (*Leuk Lymphoma.* 2004;45:2047-55).
3) Patients who achieved a minor response (MR) to the most recent treatment but experienced progressive disease (PD) thereafter.
4) Patients who experienced stable disease (SD) or PD following the most recent treatment.

7.R Outline of the review conducted by PMDA

7.R.1 Reviewing policy

PMDA concluded that, among the evaluation data submitted, the most important clinical study for evaluating the efficacy and safety of tirabrutinib was the Japanese Phase II study (Study 05) conducted in patients with WM or LPL, and decided to evaluate with a focus on this study.

7.R.2 Efficacy

On the basis of the following review, PMDA concluded that the efficacy of tirabrutinib had been demonstrated to a certain extent in patients with WM or LPL.

7.R.2.1 Efficacy endpoints and evaluation results

In both Cohort A (treatment-naïve patients) and Cohort B (recurrent or refractory patients) of Study 05, the lower limit of 95% confidence interval (CI) of the centrally-assessed response rate based on IWWM criteria, the primary endpoint, exceeded the pre-specified threshold response rate (45.0% and 20.0%, respectively) [see Section 7.1.1.1]. Figure 1 shows the maximum rate of change in serum immunoglobulin M (IgM) concentration and lymph node lesions (only in patients with measurable lesion at baseline). The median centrally-assessed response duration (in months) [95% CI], the secondary endpoint, was not applicable (NA) [NA, NA] in Cohort A and NA [5.98, NA] in Cohort B.[5)]

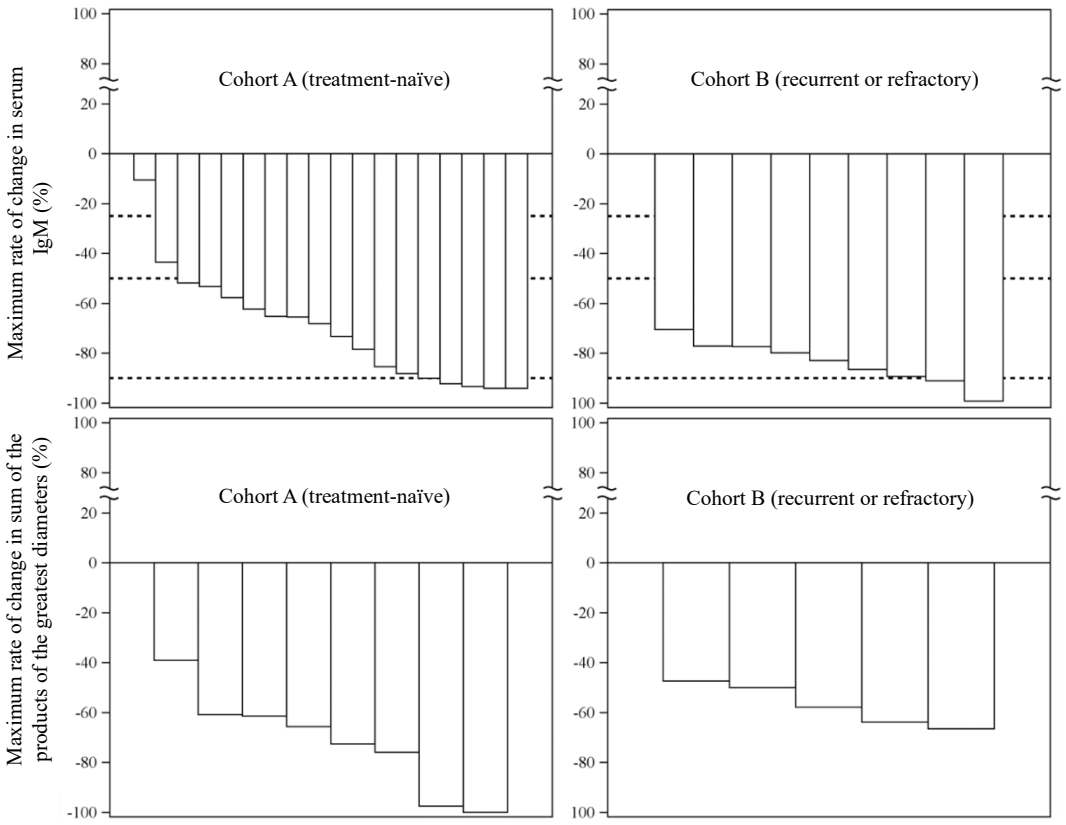

Figure 1. Maximum rate of change in serum IgM concentration (upper figure) and maximum rate of change in lymph node lesions (lower figure)
(IWWM criteria, Study 05, efficacy analysis population, centralized assessment)

[5)] The response duration ranged from 0 to 8.3 months in Cohort A and 3.5 to 6.4 months in Cohort B.

The applicant's explanation about the response rate, the primary endpoint in Study 05:
Patients with WM or LPL have poor prognosis, and there is no established standard treatment proven to prolong overall survival (OS) of these patients. Nevertheless, tumor shrinkage is expected to lead to improved clinical symptoms, and it is of clinical significance that patients with WM or LPL respond to tirabrutinib.

PMDA's view:
The applicant's explanation about the efficacy endpoints is acceptable. Accordingly, PMDA concluded that the efficacy of tirabrutinib had been demonstrated to a certain extent in patients with WM or LPL.

7.R.3 Safety

PMDA's view:
The discussions in the following subsections identifies adverse events requiring particular attention during tirabrutinib treatment in patients with WM or LPL, namely, bone marrow depression, infection, interstitial lung disease [ILD], skin disorder, hemorrhage, hepatic dysfunction, and hypersensitivity. These events had been highlighted for attention in the course of prior review for recurrent or refractory PCNSL (see "Review Report on Velexbru Tablets 80 mg dated February 6, 2020"). Caution should be exercised against these possible adverse events in the use of tirabrutinib, as practiced in the treatment for recurrent or refractory PCNSL, the approved indication.

Although the treatment requires caution against the above-mentioned adverse events, tirabrutinib will be tolerable when adverse events are appropriately monitored and controlled under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.3.1 Safety profile of tirabrutinib

The applicant's explanation about the safety profile of tirabrutinib:
Table 3 is the summary of safety in Study 05.

Table 3.Safety summary (Study 05)

	Number of patients (%)		
	All patients	Cohort A (treatment-naïve patients)	Cohort B (recurrent or refractory patients)
	n = 27	n = 18	n = 9
All adverse events	27 (100)	18 (100)	9 (100)
Grade ≥3 adverse events	8 (29.6)	4 (22.2)	4 (44.4)
Adverse events resulting in death	0	0	0
Serious adverse events	2 (7.4)	2 (11.1)	0
Adverse events leading to treatment discontinuation	1 (3.7)	1 (5.6)	0
Adverse events leading to treatment interruption	12 (44.4)	7 (38.9)	5 (55.6)
Adverse events leading to dose reduction	0	0	0

Table 4 shows adverse events of all grades with an incidence of ≥15% in either cohort in Study 05.

Table 4. Adverse events with an incidence of ≥15% in either cohort (Study 05)

SOC PT (MedDRA/J ver.21.1)	Number of patients (%)					
	All patients (n = 27)		Cohort A (treatment-naïve patients) (n = 18)		Cohort B (recurrent or refractory patients) (n = 9)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	27 (100)	8 (29.6)	18 (100)	4 (22.2)	9 (100)	4 (44.4)
Gastrointestinal disorders						
Stomatitis	4 (14.8)	0	3 (16.7)	0	1 (11.1)	0
Infections and infestations						
Nasopharyngitis	3 (11.1)	0	1 (5.6)	0	2 (22.2)	0
Bronchitis	2 (7.4)	0	0	0	2 (22.2)	0
Investigations						
Neutrophil count decreased	5 (18.5)	2 (7.4)	1 (5.6)	0	4 (44.4)	2 (22.2)
White blood cell count decreased	5 (18.5)	2 (7.4)	1 (5.6)	0	4 (44.4)	2 (22.2)
Lymphocyte count decreased	3 (11.1)	3 (11.1)	1 (5.6)	1 (5.6)	2 (22.2)	2 (22.2)
Skin and subcutaneous tissue disorders						
Rash	12 (44.4)	0	11 (61.1)	0	1 (11.1)	0
Rash maculo-papular	3 (11.1)	0	3 (16.7)	0	1 (11.1)	0

In Study 05, serious adverse events were transient ischaemic attack and rhegmatogenous retinal detachment in 1 patient each (5.6%) in Cohort A, and a causal relationship to tirabrutinib was ruled out for both events (0 in Cohort B). The adverse event leading to the discontinuation of tirabrutinib was atypical mycobacterial infection in 1 patient (5.6%) in Cohort A, and its causal relationship to tirabrutinib could not be ruled out (0 in Cohort B). Adverse events leading to the interruption of tirabrutinib observed in ≥2 patients were rash maculo-papular in 2 patients (11.1%) in Cohort A and neutrophil count decreased in 2 patients (22.2%) in Cohort B.

The applicant's explanation about the difference in the safety profiles of tirabrutinib between patients with WM or LPL and patients with recurrent or refractory primary central nervous system lymphoma (PCNSL) (approved indication):

Table 5 is the summary of safety in Study 05 in patients with WM or LPL and in Study ONO-4059-02 (Study 02[6)]) in patients with recurrent or refractory PCNSL.

Table 5 Safety summary (Studies 05 and 02)

	Number of patients (%)	
	Study 05 (n = 27)	Study 02 (480 mg fasted) (n = 17)
All adverse events	27 (100)	15 (88.2)
Grade ≥3 adverse events	8 (29.6)	10 (58.8)
Adverse events resulting in death	0	0
Serious adverse events	2 (7.4)	3 (17.6)
Adverse events leading to treatment discontinuation	1 (3.7)	0
Adverse events leading to treatment interruption	12 (44.4)	10 (58.8)
Adverse events leading to dose reduction	0	1 (5.9)

The adverse event with a ≥10% higher incidence in Study 05 than in Study 02 was nasopharyngitis (3 patients [11.1%] in Study 05, 0 patient in Study 02). The Grade ≥3 adverse event with a ≥5% higher incidence in Study 05 than in Study 02 was lymphopenia (3 [11.1%], 0). Serious adverse events with a higher incidence in Study 05 than in Study 02 were transient ischaemic attack (1 [3.7%], 0) and

6) Data obtained from patients receiving tirabrutinib 480 mg (fasted), the dosage regimen identical with that in Study 05.

rhegmatogenous retinal detachment (1 [3.7%], 0). The adverse event leading to treatment discontinuation with a higher incidence in Study 05 than in Study 02 was atypical mycobacterial infection (1 [3.7%], 0). The adverse event leading to treatment interruption with a ≥5% higher incidence in Study 05 than in Study 02 was neutrophil count decreased (2 [7.4%], 0). There was no adverse event leading to death or dose reduction with a higher incidence in Study 05 than in Study 02.

PMDA's view:
Caution should be exercised against serious adverse events and Grade ≥3 adverse events observed in Study 05 and adverse events with a higher incidence in Study 05 than in Study 02. However, given that all these adverse events are known events of tirabrutinib treatment, tirabrutinib will be tolerable in patients with WM or LPL when events are appropriately monitored and controlled under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.4 Clinical positioning and indication

The proposed indication of tirabrutinib was "Waldenström's macroglobulinemia and lymphoplasmacytic lymphoma."

As a result of discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following subsection, PMDA concluded that the indication should be specified as proposed by the applicant.

7.R.4.1 Clinical positioning and indication of tirabrutinib

Japanese or foreign clinical practice guidelines[7)] or major international textbooks[8)] on clinical oncology or hematology provide no descriptions of tirabrutinib in the treatment of WM or LPL.

PMDA asked the applicant to explain the clinical positioning and indication of tirabrutinib.

The applicant's explanation:
WM, a subtype of LPL, is characterized by bone marrow infiltration and IgM-proteinemia. WM and LPL are both extremely rare and refractory diseases. Currently, Japanese textbooks and the clinical practice guidelines[9)] recommend to treat patients with treatment-naïve WM or LPL with rituximab, alkylating agents, purine analogs, or bortezomib alone or in combination with these antineoplastic agents. Foreign textbooks and clinical practice guidelines[10)] recommend, on top of these treatments, ibrutinib alone or in combination with rituximab.[11)] For patients with recurrent or refractory WM or LPL, the use of the first-line therapy or high-dose chemotherapy with hematopoietic stem cell transplantation is recommended.

---

7) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (NCCN Guidelines). v.1.2020. Clinical Practice Guidelines for Hematologic Malignancy. Japanese Society of Hematology. 2018.

8) *Wintrobe's Clinical Hematology*. 14th Edition (Netherlands: Wolters Kluwer; 2019). *Williams Hematology*. 9th Edition (USA: The McGraw-Hill Company, Inc.; 2016).

9) Textbook for Hematologist (third revision) and Clinical Practice Guidelines for Hematologic Malignancy, 2018 (Japanese Society of Hematology).

10) NCCN Guidelines (v.1.2020), US National Cancer Institute Physician Data Query, Ewing Sarcoma Treatment (NCI-PDQ) (September 18, 2019), *Harrison's Principles of Internal Medicine*. 20th edition (USA: McGraw-Hill Education; 2018). *Wintrobe's Clinical Hematology*. 14th Edition (Netherlands: Wolters Kluwer; 2019). *Williams Hematology*. 9th Edition (USA: The McGraw-Hill Company, Inc.; 2016).

11) Currently, ibrutinib is not approved for WM or LPL in Japan.

However, none of the above treatments have been subjected to confirmatory clinical studies, leaving no standard treatment established.

In this situation, the clinical usefulness of tirabrutinib was demonstrated in Study 05 in patients with treatment-naïve, recurrent, or refractory WM and LPL [see Sections 7.R.2 and 7.R.3]. These results suggest that tirabrutinib is expected to be a treatment option for these patients. In Study 05, which enrolled 26 patients with WM and 1 patient with LPL, the response rate was 88.5% (23 of 26 patients) and 100% (1 of 1 patient), respectively. There was no clear difference in safety profiles between these patient groups.

Based on the above, the appropriate indication is "Waldenström's macroglobulinemia and lymphoplasmacytic lymphoma."

PMDA accepted the explanation of the applicant.

7.R.5 Dosage and administration

The proposed dosage regimen of tirabrutinib was "the usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition." Meanwhile, after the submission of present partial change application, the descriptions of the "Precautions Concerning Dosage and Administration" section were specified as follows[12)] by the applicant, with modified guidelines for treatment interruption, dose reduction, and discontinuation in case of adverse drug reactions.

Precautions Concerning Dosage and Administration

- The efficacy and safety of tirabrutinib used in combination with other antineoplastic agents have not been established.
- It is reported that C_{max} and AUC of tirabrutinib increase when tirabrutinib is administered after a meal. In order to avoid the food effect, use of tirabrutinib should be avoided from 1 hour before until 2 hours after a meal.
- If adverse drug reactions occur following the treatment, tirabrutinib should be interrupted, reduced in dose, or discontinued according to the following criteria.

Level of tirabrutinib dose reduction

Level	Dose
Usual dose	480 mg
1-level lower dose	320 mg
2-level lower dose	160 mg

12) The descriptions remain unchanged from precautions concerning dosage and administration for the approved indication.

Guidelines for treatment interruption, dose reduction, and discontinuation in case of adverse drug reactions

Adverse drug reaction*		Measures to be taken
Grade 4 neutropenia		Interrupt tirabrutinib until recovery to Grade ≤3. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.
Grade 3 thrombocytopenia with hemorrhage		Interrupt tirabrutinib until recovery to Grade ≤2. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.
Grade 4 thrombocytopenia		
Grade ≥3 hematotoxicity (other than thrombocytopenia and neutropenia)		
Grade ≥3 nonhematological toxicity (other than ILD and skin disorder)		
ILD	Grade 2 or 3	Interrupt tirabrutinib until recovery to Grade ≤1. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.
	Grade 4	Discontinue tirabrutinib.
Skin disorder	Grade 2	Administer antihistamine, adrenocorticosteroid, etc. If resolved, continue tirabrutinib. If the symptom does not resolve, continue tirabrutinib at 1-level lower dose or interrupt tirabrutinib.
	Grade ≥3	Administer antihistamine, adrenocorticosteroid, etc., and interrupt tirabrutinib until recovery to Grade ≤2. After recovery, tirabrutinib may be resumed at 1-level lower dose.

* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0.

As a results of discussion in the Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the discussion in the following subsection, PMDA concluded that the Dosage and Administration and Precautions Concerning Dosage and Administration sections should be defined as proposed by the applicant.

7.R.5.1 Dosage and administration of tirabrutinib

The applicant's explanation about the dosage regimen of tirabrutinib:

The Japanese and foreign Phase I studies demonstrated the tolerability of tirabrutinib 480 mg QD while suggesting the effect of food intake on tirabrutinib (see "Review Report on Velexbru Tablets 80 mg dated February 6, 2020"). Thus, in Study 05, tirabrutinib was administered at 480 mg QD (fasted) and demonstrated its clinical usefulness in patients with WM or LPL. Consequently, the dosage regimen used in Study 05 was proposed for approval.

PMDA accepted the explanation of the applicant.

7.R.6 Post-marketing investigations

The applicant's explanation about the plan for post-marketing investigations:

In order to investigate the safety, etc., of tirabrutinib in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance targeting all patients with WM or LPL who are treated with tirabrutinib.

The safety specification in the surveillance remains unchanged from that (infection, severe skin disorder, bone marrow depression, hypersensitivity, ILD, hepatic dysfunction, and hemorrhage) in the post-marketing surveillance (all-case surveillance) for the approved indication (recurrent or refractory PCNSL) based on the following view point:

- Study 05 revealed higher incidence of some adverse events than in the Japanese Phase II study (Study 02) in patients with recurrent or refractory PCNSL, the approved indication. However, all of them were known events of tirabrutinib, suggesting no new safety concerns in administering tirabrutinib to patients with WM or LPL [see Section 7.R.3].

The planned sample size is 60 patients based on the incidences, etc. in Study 05 of events included in the above safety specification.

The follow-up period is 52 weeks, because most of the events included in the safety specification occurred within 52 weeks after the start of treatment in Study 05.

PMDA's view:
Taking into account of (a) extremely limited safety information of patients with WM or LPL treated with tirabrutinib and (b) the yet unavailable result of post-marketing surveillance in patients with recurrent or refractory PCNSL, the surveillance should be conducted covering all patients with WM or LPL treated with tirabrutinib for a certain period after market launch, to collect safety data promptly in an unbiased manner and provide healthcare professionals with obtained safety information without delay.

The safety specification of the surveillance, the planned sample size, and the follow-up period planned by the applicant are acceptable.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application document submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that tirabrutinib has efficacy in the treatment of WM and LPL, and that tirabrutinib has acceptable safety in view of its benefits. Tirabrutinib is thus expected to be of clinical significance as a treatment option for WM and LPL. The efficacy, clinical positioning, indication, etc., should be further evaluated.

PMDA has concluded that tirabrutinib may be approved if tirabrutinib is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

June 25, 2020

Product Submitted for Approval

Brand Name	Velexbru Tablets 80 mg
Non-proprietary Name	Tirabrutinib Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	April 7, 2020

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of its discussion in Section "7.R.2 Efficacy" in the Review Report (1), PMDA concluded that a certain level of efficacy of tirabrutinib was demonstrated in patients with WM and patients with LPL on the basis of "response rate [95% CI] according to the centralized assessment based on IWWM criteria," the primary endpoint, in Cohort A (treatment-naïve patients) and in Cohort B (recurrent or refractory patients) of the Japanese Phase II study (Study 05). The result was 88.9% [65.3%, 98.6%] in Cohort A and 88.9% [51.8%, 99.7%] in Cohort B, with the lower limit of 95% CI exceeding the pre-defined threshold response rate (45.0% in Cohort A and 20.0% in Cohort B).

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the discussion in Section "7.R.3 Safety" in the Review Report (1), PMDA concluded that the use of tirabrutinib requires attention to adverse events, namely, bone marrow depression, infection, ILD, skin disorder, hemorrhage, hepatic dysfunction, and hypersensitivity, which were identified for attention in the course of prior review for recurrent or refractory PCNSL.

PMDA also concluded that although the treatment requires caution against the above-mentioned adverse events, tirabrutinib will be tolerable when adverse events are appropriately monitored and controlled under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

After the discussion in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), PMDA concluded that the indication of tirabrutinib should be defined as "Waldenström's macroglobulinemia and lymphoplasmacytic lymphoma" as proposed because tirabrutinib is expected to become a treatment option for treatment-naïve, or recurrent or refractory WM and LPL.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.4 Dosage and administration

After the discussion in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections be described as below.

Dosage and Administration

The usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of tirabrutinib used in combination with other antineoplastic agents have not been established.
- It is reported that C_{max} and AUC of tirabrutinib increase when administered after a meal. In order to avoid the food effect, the use of tirabrutinib should be avoided from 1 hour before until 2 hours after a meal.
- Guidelines for dose adjustment in case of adverse drug reactions

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.5 Risk management plan (draft)

In order to investigate the safety of tirabrutinib in its post-marketing clinical use, the applicant plans to conduct post-marketing surveillance targeting all patients with WM or LPL who are on tirabrutinib. The planned sample size is 60 patients and the follow-up period is 52 weeks.

After the discussion in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA concluded that post-marketing surveillance should be conducted covering all patients with WM or LPL receiving tirabrutinib for a certain period after market launch, during which safety data should be collected promptly and in an unbiased manner and obtained safety findings should be provided to healthcare professionals without delay.

The safety specification in the surveillance, the planned target sample size, and the follow-up period proposed by the applicant are acceptable.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) should include the safety specification presented in Table 6, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 7 and 8.

Table 6. Safety and efficacy specifications in risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infection • Severe skin disorder • Bone marrow depression • Hypersensitivity • ILD • Hepatic dysfunction • Hemorrhage	• Embryo-fetal toxicity	Not applicable
Efficacy specification		
Not applicable		

No change in the present partial change application

Table 7. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance (recurrent or refractory PCNSL) • Early post-marketing phase vigilance (WM and LPL) • Specified drug use-results survey (all-case surveillance) in patients with recurrent or refractory PCNSL • Specified drug use-results survey (all-case surveillance) in patients with WM or LPL • Post-marketing clinical studies (extension of Study 02 [tirabrutinib 480 mg QD (fasted) only], Study ONO-4059-02E,[*1] Study 05, and Study ONO-4059-05E[*2])	Not applicable	• Information provision based on the early post-marketing phase vigilance (recurrent or refractory PCNSL) • Information provision based on the early post-marketing phase vigilance (WM and LPL) • Preparation and distribution of materials for healthcare professionals

*1, A compassionate study focused mainly on Study 02; *2, A compassionate study focused mainly on Study 05
Underlined part, Activities to be conducted on the indication added in the present application.

Table 8. Outline of use-results survey plan (draft)

Objective	To investigate the safety of tirabrutinib in clinical use
Survey method	All-case surveillance
Population	All patients with WM or LPL receiving tirabrutinib
Follow-up period	52 weeks
Planned sample size	60
Main survey items	Safety specification: Infection, severe skin disorder, bone marrow depression, hypersensitivity, ILD, hepatic dysfunction, and hemorrhage Other main survey items: Patient characteristics (age, sex, past illness, comorbidities, etc.), status of tirabrutinib administration, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that tirabrutinib may be approved for the indications and dosage and administration shown below, with the following approval conditions. The approval however presupposes cautionary advice given via the package insert and information on the proper use of the product provided appropriately in the post-marketing setting, as well as strict adherence

to the proper use of the product under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy at medical institutions capable of an emergency response. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until March 24, 2030).

Indications (Underline denotes additions.)
○ Recurrent or refractory primary central nervous system lymphoma
○ Waldenström's macroglobulinemia and lymphoplasmacytic lymphoma

Dosage and Administration (No change)
The usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition.

Approval Conditions
1. The applicant is required to develop and appropriately implement a risk management plan.

2. Because of extremely limited number of cases in Japanese clinical studies, the applicant is required to conduct a drug use-results survey involving all patients treated with the product after its market launch until obtaining data from a certain number of patients, in order to identify the characteristics of patients using the product and to promptly collect safety and efficacy data so as to take necessary measures for the proper use of the product.

Warning (No change)
The product should be administered only to patients recognized as eligible for the treatment with the product by a physician with adequate knowledge and experience in cancer chemotherapy at a medical institution capable of an emergency response. Prior to treatment, patients or their family members should be thoroughly informed of the potential risks and benefits of the treatment and provide consent.

Contraindication (No change)
Patients with a history of hypersensitivity to any ingredient of the product.

Precautions Concerning Indications (Underline denotes additions.)
Recurrent or refractory primary central nervous system lymphoma
Physicians should be well-versed in the findings presented in the "Clinical Studies" section to have a full understanding of the efficacy and safety of tirabrutinib before selecting eligible patients.

Precautions Concerning Dosage and Administration (Underline denotes additions, and strikethrough denotes deletions.)
1. The efficacy and safety of tirabrutinib used in combination with other antineoplastic agents have not been established.

2. It is reported that C_{max} and AUC of tirabrutinib increase when administered after a meal. In order to avoid the food effect, the use of tirabrutinib should be avoided from 1 hour before until 2 hours after a meal.

3. If adverse drug reactions occur following the treatment, tirabrutinib should be interrupted, reduced in dose, or discontinued according to the following criteria.

Level of tirabrutinib dose reduction

Level	Dose
Usual dose	480 mg
1-level lower dose	320 mg
2-level lower dose	160 mg

Guidelines for treatment interruption, dose reduction, and discontinuation in case of adverse drug reactions

Adverse drug reaction*		Measures to be taken
Grade 4 neutropenia		Interrupt tirabrutinib until recovery to Grade ≤3. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.
~~Grade ≥3 febrile neutropenia~~ Grade 3 thrombocytopenia with hemorrhage ~~Grade 4 neutropenia~~ ~~Grade 4 thrombocytopenia~~		Interrupt tirabrutinib until recovery to Grade ≤2~~ (Grade ≤3 for neutropenia)~~. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.
Grade 4 thrombocytopenia		
Grade ≥3 hematotoxicity (other than thrombocytopenia and neutropenia)		
Grade ≥3 nonhematological toxicity (other than interstitial lung disease and skin disorder)		
Interstitial lung disease	Grade 2 or 3	Interrupt tirabrutinib until recovery to Grade ≤1. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.
	Grade 4	Discontinue tirabrutinib.
Skin disorder	Grade 2	Administer antihistamine, adrenocorticosteroid, etc. If resolved, continue tirabrutinib. If the symptom does not resolve, continue tirabrutinib at 1-level lower dose or interrupt tirabrutinib.
	Grade ≥3	Administer antihistamine, adrenocorticosteroid, etc., and interrupt tirabrutinib until recovery to Grade ≤2. After recovery, tirabrutinib may be resumed at 1-level lower dose.
~~Grade ≥3 hematotoxicity (other than events described above) and Grade ≥3 nonhematological toxicity (other than interstitial lung disease and skin disorder)~~		~~Interrupt tirabrutinib until recovery to Grade ≤2.~~ ~~After recovery, tirabrutinib may be resumed at the dose before interruption.~~ ~~If the symptom recurs after resumption, interrupt tirabrutinib until recovery.~~ ~~After recovery, tirabrutinib may be resumed at a 1-level lower dose.~~

* Graded according to NCI-CTCAE v4.0.

List of Abbreviations

BCR	B cell receptor
BID	bis in die
B-NHL	B-cell non-Hodgkin lymphoma
BTK	Bruton's tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
Fludarabine	fludarabine phosphate
IgM	immunoglobulin M
ILD	interstitial lung disease
IWWM	International Workshop on Waldenström's Macroglobulinemia
LPL	lymphoplasmacytic lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MR	Minor response
NA	not applicable
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-PDQ	National Cancer Institute Physician Data Query, Ewing Sarcoma Treatment
OS	overall survival
Partial change application	Application for partial changes in the approved application
PCNSL	primary central nervous system lymphoma
PD	progressive disease
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
QD	quaque die
Rituximab	rituximab (genetical recombination)
SD	stable disease
SOC	system organ class
Study 01	Study ONO-4059-01
Study 02	Study ONO-4059-02
Study 04	Study ONO-4059-04
Study 05	Study ONO-4059-05
Study 1765	Study GS-US-401-1765
Study 1767	Study GS-US-401-1767
Study 1768	Study GS-US-401-1768
Study POE001	Study ONO-4059POE001
Tirabrutinib	tirabrutinib hydrochloride
VGPR	very good partial response
WM	Waldenström's macroglobulinemia