Report on the Deliberation Results

February 17, 2017

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Revlimid Capsules 2.5 mg, Revlimid Capsules 5 mg
Non-proprietary Name	Lenalidomide Hydrate (JAN*)
Applicant	Celgene K.K.
Date of Application	June 24, 2016

Results of Deliberation

In its meeting held on February 3, 2017, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Conditions of Approval

1. The applicant is required to comply with "the procedures for proper management of Revlimid and Pomalyst" in the production, control, and use of the product. Any modification to the procedures is subject to the pre-approval by the Ministry of Health, Labour and Welfare.

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

3. The applicant is required to ensure by strict and appropriate means that the product is used only for patients recognized as eligible for the therapy, under the supervision of a knowledgeable and experienced physician at a medical institution well-prepared for emergency care. The benefits and risks of the product must be explained to the patient or their family member in a written form and written consent must be obtained prior to the therapy.

* *Japanese Accepted Name (modified INN)*

Review Report

January 16, 2017

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.

Brand Name	Revlimid Capsules 2.5 mg, Revlimid Capsules 5 mg
Non-proprietary Name	Lenalidomide Hydrate
Applicant	Celgene K.K.
Date of Application	June 24, 2016
Dosage Form/Strength	Capsules, each containing 2.587 or 5.174 mg of Lenalidomide Hydrate (2.5 or 5 mg of lenalidomide).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Drug Designation No. 384 of 2016 [*28 yaku*]; PSEHB/PED Notification No. 0620-4 dated June 20, 2016 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 relapsed or refractory adult T cell leukemia-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 indication and dosage and administration shown below, with the following conditions.

Indications

1. Multiple myeloma
2. Myelodysplastic syndromes associated with a deletion 5q abnormality
3. Relapsed or refractory adult T cell leukemia-lymphoma

(Underline denotes addition.)

Dosage and Administration

1. Multiple myeloma

In combination with dexamethasone, the usual adult dosage is 25 mg of lenalidomide administered orally once daily for 21 days, followed by a 7-day withdrawal period. This treatment cycle is repeated. The dose may be reduced according to the condition of the patient.

2. Myelodysplastic syndromes associated with a deletion 5q abnormality

The usual adult dosage is 10 mg of lenalidomide administered orally once daily for 21 days, followed by a 7-day withdrawal period. This treatment cycle is repeated. The dose may be reduced according to the condition of the patient.

3. Relapsed or refractory adult T cell leukemia-lymphoma

The usual adult dosage is 25 mg of lenalidomide administered orally once daily. The dose may be reduced according to the condition of the patient.

(Underline denotes addition.)

Conditions of Approval

1. The applicant is required to comply with "the procedures for proper management of Revlimid and Pomalyst" in the production, control, and use of the product. Any modification to the procedures is subject to the pre-approval by the Ministry of Health, Labour and Welfare.

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

3. The applicant is required to ensure by strict and appropriate means that the product is used only for patients recognized as eligible for the therapy, under the supervision of a knowledgeable and experienced physician at a medical institution well-prepared for emergency care. The benefits and risks of the product must be explained to the patient or their family member in a written form and written consent must be obtained prior to the therapy.

Attachment

Review Report (1)

November 28, 2016

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	Revlimid Capsules 2.5 mg, Revlimid Capsules 5 mg
Non-proprietary Name	Lenalidomide Hydrate
Applicant	Celgene K.K.
Date of Application	June 24, 2016
Dosage Form/Strength	Capsules, each containing 2.587 or 5.174 mg of Lenalidomide Hydrate (2.5 or 5 mg of lenalidomide).
Proposed Indications	1. Multiple myeloma 2. Myelodysplastic syndromes associated with a deletion 5q abnormality 3. Relapsed or recrudescent adult T cell leukemia-lymphoma (Underline denotes addition.)

Proposed Dosage and Administration

1. Multiple myeloma
   In combination with dexamethasone, the usual adult dosage is 25 mg of lenalidomide administered orally once daily for 21 days, followed by a 7-day withdrawal period. This treatment cycle is repeated. The dose may be reduced according to the condition of the patient.

2. Myelodysplastic syndromes associated with a deletion 5q abnormality
   The usual adult dosage is 10 mg of lenalidomide administered orally once daily for 21 days, followed by a 7-day withdrawal period. This treatment cycle is repeated. The dose may be reduced according to the condition of the patient.

3. Relapsed or recrudescent adult T cell leukemia-lymphoma
   The usual adult dosage is 25 mg of lenalidomide administered orally once daily. The dose may be reduced according to the condition of the patient.

(Underline denotes addition.)

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List of Abbreviations

Ae_{24h}	cumulative amount excreted in urine from 0-24 hours after a dose
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATLL	adult T-cell leukemia/lymphoma
CCR4	CC chemokine receptor 4
CI	confidence interval
CL_r	renal clearance
CR	complete response
CRBN	cereblon
Criteria of International Conference on Human Retrovirology	criteria discussed at the 13th International Conference on Human Retrovirology
CRu	complete response unconfirmed
DLT	dose limiting toxicity
ESEC	Efficacy Safety Evaluation Committee
Fe_{24h}	cumulative fraction of administered dose excreted unchanged in urine 0-24 hours after a dose
GVHD	graft versus host disease
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
HTLV-1	human T-cell leukemia virus type 1
Japanese Clinical Practice Guidelines	Clinical Practice Guidelines for Hematologic Malignancy 2013, edited by Japanese Society of Hematology (Kanehara & Co. Ltd., 2013)
JCOG-LSG	Japan Clinical Oncology Group-Lymphoma Study Group
Lenalidomide	lenalidomide hydrate
MDS	myelodysplastic syndrome
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MM	multiple myeloma
Mogamulizumab	mogamulizumab (genetical recombination)
MTD	maximum tolerated dose
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas
NCI-PDQ	National Cancer Institute Physician Data Query
NE	not evaluated
Partial change application	Application for partial change approval
PD	progressive disease
PGA	physician's global assessment
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
PTCL	peripheral T-cell lymphoma
QD	quaque die
RD	relapsed disease
SCID mice	severe combined immunodeficiency mice
SD	stable disease
SOC	system organ class
Study ATLL-001	Study CC-5013-ATLL-001
Study ATLL-002	Study CC-5013-ATLL-002
Study MDS-007	Study CC-5013-MDS-007
Study MM-017/022	Studies CC-5013-MM-017 and CC-5013-MM-022
Study MM-025	Study CC-5013-MM-025

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

1.1 Outline of the product submitted for approval

Lenalidomide hydrate (to be referred to as lenalidomide) is an antineoplastic agent discovered by Celgene Corporation (the US) as a derivative of thalidomide, a compound known to be teratogenic in humans (thalidomide embryopathy; limb malformation such as amelia, phocomelia, and ectromelia; cardiac disease; visceral disorders such as obstruction of the gastrointestinal system; etc.). Toxicology studies in cynomolgus monkeys suggested that lenalidomide may be teratogenic, and its chemical structure and nonclinical study results indicate the possibility that the administration of lenalidomide during pregnancy may cause serious fetal malformation, abortion, or stillbirth in humans as well.

Like thalidomide, lenalidomide induces apoptosis, suppresses the production of cytokines such as tumor necrosis factor (TNF)-α, activates T lymphocytes and natural killer cells, and suppresses angiogenesis. Lenalidomide is expected to inhibit tumor growth through these actions.

In Japan, lenalidomide was approved for the indication for "relapsed or refractory multiple myeloma" in June 2010, for "myelodysplastic syndromes associated with a deletion 5q abnormality" in August 2010, and for "multiple myeloma" in December 2015.

1.2 Development history, etc.

For the clinical development of lenalidomide against adult T-cell leukemia/lymphoma (ATLL), a Japanese phase I study (Study CC-5013-ATLL-001 [Study ATLL-001]) in patients with previously treated ATLL or peripheral T-cell lymphoma (PTCL) began in July 2010. After that, a Japanese phase II study (Study CC-5013-ATLL-002 [Study ATLL-002]) in patients with relapsed or recrudescent ATLL began in November 2012. As of June 2016, the development of lenalidomide for the treatment of ATLL has not been undertaken in foreign countries.

Recently, a partial change application has been submitted for the additional indication of ATLL, based on the results of Study ATLL-002 as the pivotal data.

Lenalidomide was designated as an orphan drug with the expected indication of "relapsed or refractory adult T cell leukemia-lymphoma" in June 2016 (Drug Designation No. 384 of 2016 [*28 yaku*]).

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

Since the current application relates to a new indication and a new dosage, "data relating to quality" were not submitted.

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

3.1 Primary pharmacodynamics

3.1.1 Growth-inhibitory effect against malignant tumor-derived cell lines

3.1.1.1 *In vitro* (CTD 4.2.1.1.1)

A growth-inhibitory effect of lenalidomide (0.1, 1.0, 10, or 100 μmol/L) against various cell lines was investigated using reductase activity in viable cells as the index. The cell lines used were human ATLL-derived HuT102, ED40515, Su9T1, OATL4, OATL9, S1T, ST1, KOB, KK1, and SO4 cell lines; human cutaneous T-cell lymphoma-derived HuT78 cell line; human leukemia-derived MOLT4, Jurkat, K562, and HL60 cell lines; and human T-cell leukemia virus type 1 (HTLV-1)-infected human umbilical cord blood-derived MT-2, MT-4, and C8166 cell lines. Lenalidomide inhibited the growth of OATL4 and KOB cell lines by up to 32%, showing a statistically significant inhibitory effect against HuT102 cell line ($P < 0.05$, t-test). In contrast, lenalidomide did not show an inhibitory effect against other cell lines.

In this study, the expression levels of cereblon (CRBN) in HuT102 (a cell line sensitive to lenalidomide) and in HuT78 (a cell line insensitive to lenalidomide) were investigated by Western blotting. The CRBN expression level was high in HuT102 cell line as compared with HuT78 cell line.

3.1.1.2 *In vivo* (CTD 4.2.1.1.2)

Using severe combined immunodeficiency (SCID) mice (n = 5 or 6/group) subcutaneously transplanted with HuT102 cell line, a growth-inhibitory effect of lenalidomide was investigated. Starting from the day of transplantation or from Day 11 after transplantation (tumor volume, approximately 100 mm^3),

lenalidomide (10, 50, 100 mg/kg) was administered orally quaque die (QD) for 28 days, and tumor volume was calculated. A statistically significant tumor growth-inhibitory effect ($P < 0.05$, Dunnett's test) was observed in mice in all lenalidomide groups compared with those in the control (aqueous solution of 0.5% carboxymethyl cellulose and 0.25% polysorbate 80) group at the end of lenalidomide administration regardless of the starting day of administration.

3.R Outline of the review conducted by PMDA

PMDA has concluded that the data submitted and the following observations indicate promising efficacy of lenalidomide against ATLL.

3.R.1 Mechanism of action and efficacy of lenalidomide against ATLL

According to the applicant, lenalidomide is expected to exhibit a tumor growth-inhibitory effect against ATLL by an action mechanism similar to that against multiple myeloma (MM) (see "Review Report on Revlimid Capsules 5 mg, dated May 12, 2010").

The applicant provided the following findings indicating the expression level of CRBN may have affected the efficacy of lenalidomide against ATLL, as reasons for not showing a growth-inhibitory effect against some of ATLL-derived cell lines studied [see Section "3.1.1.1 *In vitro*"]:

- CRBN is reported to play an important role in part of the pharmacological effect of lenalidomide (*Blood.* 2011;118:4771-9, *Leukemia*. 2012;26:2326-35).
- The expression level of CRBN was different between lenalidomide-sensitive cell lines and insensitive cell lines [see Section "3.1.1.1 *In vitro*"].

PMDA's view:

Although the detailed molecular mechanism of how lenalidomide inhibits the growth of ATLL-derived tumor cells is unclear, lenalidomide may be effective against ATLL, because lenalidomide inhibited the growth of some of ATLL-derived cell lines studied. However, the CRBN expression level in ATLL-derived cell lines resistant to the growth-inhibitory effect of lenalidomide was not determined, and thus the applicant's explanation about the relationship between the CRBN expression level and the efficacy of lenalidomide against ATLL seems to be inadequate.

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

The current application relates to a new indication and a new dosage, and no new study data were submitted on the ground that "data on non-clinical pharmacokinetics" were evaluated at the initial application.

5. Toxicity and Outline of the Review Conducted by PMDA

The current application relates to a new indication and a new dosage, and no new study data were submitted on the ground that "toxicity data" were evaluated at the initial application.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Assay

Lenalidomide in human plasma and urine samples was assayed by LC-MS/MS. The lower limit of quantitation was 5 and 100 ng/mL, respectively.

6.2 Clinical pharmacology

The pharmacokinetics (PK) of lenalidomide in patients with ATLL or PTCL was investigated after the administration of lenalidomide alone.

6.2.1 Japanese phase I study (CTD 5.3.3.2.1, Study ATLL-001 [July 2010 to December 2013])

An open-label, uncontrolled study was conducted in 14 patients with previously treated ATLL or PTCL (13 patients included in PK analysis) to investigate the PK, etc. of lenalidomide. Lenalidomide (25 or 35 mg) was administered orally QD, and plasma and urine lenalidomide concentrations were investigated (Table 1). AUC and C_{max} of lenalidomide calculated from plasma lenalidomide concentration increased roughly dose proportionally within the dose range tested, showing no

accumulation due to multiple doses. Cumulative amount excreted in urine from 0 to 24 hours after a dose (Ae_{24h}) based on urine lenalidomide concentration increased roughly dose proportionally within the dose range tested, and showed no clear difference either in Ae_{24h} or in cumulative fraction of administered dose excreted unchanged in urine 0-24 hours after a dose (Fe_{24h}) between single-dose and multiple-dose administration.

Table 1. PK parameters of lenalidomide

	25 mg		35 mg	
	Day 1 N = 9	Day 8 N = 8	Day 1 N = 4	Day 8 N = 4
C_{max} (ng/mL)	493 ± 72.6	503 ± 82.8	765 ± 301	853 ± 436
t_{max}* (h)	1.03 (0.92, 2.02)	1.02 (0.95, 2.97)	0.95 (0.92, 1.97)	0.99 (0.83, 2.93)
AUC_{24h} (ng·h/mL)	2623 ± 945.6	2782 ± 1010	3170 ± 434.0	3550 ± 1127
AUC_{∞} (ng·h/mL)	2658 ± 992.9	-	3182 ± 439.4	-
$t_{1/2, z}$ (h)	3.36 ± 0.90	3.56 ± 0.88	2.74 ± 0.75	3.45 ± 0.80
CL/F (mL/min)	175 ± 55.2	165 ± 47.8	186 ± 26.1	176 ± 52.1
Vz/F (L)	47.2 ± 5.59	48.0 ± 9.05	43.8 ± 10.7	50.9 ± 11.2
Ae_{24h} (mg)	20.0 ± 3.88	19.0 ± 2.27	25.3 ± 2.08	24.7 ± 3.02
Fe_{24h} (%)	80.2 ± 15.5	76.1 ± 9.06	72.3 ± 5.95	70.5 ± 8.62
CL_r (mL/min)	143 ± 60.0	127 ± 42.8	135 ± 21.5	124 ± 42.2

Mean ± standard deviation (SD); * Median (range); -, not applicable

6.2.2 Difference in the PK of lenalidomide between patients with MM and patients with ATLL

The applicant's explanation about the difference in the PK of lenalidomide between patients with MM and patients with ATLL:

Based on the data of patients with ATLL in Study ATLL-001 and on the PK parameter data obtained from the Japanese phase I study in patients with MM (Study CC-5013-MM-017) (see "Review Report on Revlimid Capsules 5 mg, dated May 12, 2010"), difference in the PK of lenalidomide between patients with ATLL and patients with MM was investigated. No clear difference was observed in the PK of lenalidomide between patients with ATLL and patients with MM (Table 2).

Table 2. PK parameters following a single dose of lenalidomide (25 mg)

	Patients with ATLL N = 6	Patients with MM N = 6
C_{max} (ng/mL)	503 ± 80.8	642 ± 163
t_{max}* (h)	1.06 (0.92, 2.00)	1.01 (0.43, 2.00)
AUC_{∞} (ng·h/mL)	2800 ± 1136	2867 ± 1099
$t_{1/2, z}$ (h)	3.51 ± 1.04	3.20 ± 0.83
CL/F (mL/min)	169 ± 61.2	162 ± 52.6
Vz/F (L)	46.8 ± 6.14	42.0 ± 8.52

Mean ± SD; * Median (range)

6.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the applicant's explanation about the PK of lenalidomide is acceptable.

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

The applicant submitted efficacy and safety evaluation data comprising the results from 2 Japanese clinical studies, 1 Japanese phase I study and 1 Japanese phase II study, as shown in Table 3.

Table 3. List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Subjects	No. of enrollment	Dosage regimen	Primary endpoints
Evaluation	Japan	ATLL-001	I	Patients with previously treated ATLL or PTCL	14 (a) 3 (b) 7 (c) 4	In each 28-day cycle, (a) Lenalidomide (25 mg) orally QD from Day 1 to Day 21 (b) Lenalidomide (25 mg) orally QD from Day 1 to Day 28 (c) Lenalidomide (35 mg) orally QD from Day 1 to Day 28	Safety PK
		ATLL-002	II	Patients with relapsed or recrudescent ATLL	26	Lenalidomide (25 mg) orally QD	Efficacy Safety

The outline of each clinical study is described below. Main adverse events observed in each clinical study, except death, are described in Section "7.2 Adverse events observed in clinical studies," and PK-related data are described in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese phase I study (CTD 5.3.5.2.2, Study ATLL-001 [July 2010 to December 2013])

An open-label, uncontrolled study was conducted in patients with previously treated ATLL or PTCL (target sample size, 9-18 [3-6 per cohort]) to investigate the safety, etc. of lenalidomide in 6 study centers in Japan.

In each 28-day treatment cycle, lenalidomide was administered orally according to the following regimen: (a) 25 mg QD for 21 days, followed by a 7-day withdrawal period in Cohort 1, (b) 25 mg QD daily in Cohort 2, and (c) 35 mg QD daily in Cohort 3. Lenalidomide treatment was continued until disease progression or the discontinuation criteria met.

Of 14 patients enrolled in the study (3 in Cohort 1, 7 in Cohort 2, and 4 in Cohort 3), 13 patients receiving lenalidomide (3 in Cohort 1, 6 in Cohort 2, 4 in Cohort 3) were included in the safety analysis population.

Dose limiting toxicity (DLT) was evaluated in Cycle 1. DLT was observed in none of the patients in Cohort 1, 1 of 6 patients in Cohort 2 (Grade 4 platelet count decreased), and 2 of 4 patients in Cohort 3 (Grade 3 fatigue/Grade 4 platelet count decreased and Grade 3 electrocardiogram QT prolonged in 1 patient each). The maximum tolerated dose (MTD)[1)] of lenalidomide in patients with previously treated ATLL or PTCL was determined as 25 mg QD daily.

The safety analysis revealed deaths of 2 of 13 patients (15.4%) during the treatment period or within 28 days after the end of the administration. The cause of death other than disease progression was haemorrhage intracranial in 1 patient, and its causal relationship to lenalidomide was ruled out.

7.1.2 Japanese phase II study (CTD 5.3.5.2.1, Study ATLL-002 [Ongoing since November 2012 (data cut-off November 20, 2014)])

An open-label, uncontrolled study was conducted in patients with relapsed or recrudescent[2)] ATLL[3)] (target sample size, 25) to investigate the efficacy and safety of lenalidomide in 20 study centers in Japan.

Lenalidomide 25 mg was administered orally QD daily. The treatment was continued until disease progression or the discontinuation criteria met.

Lenalidomide was administered to all 26 patients enrolled in the study, and all of them were included in both efficacy and safety analyses.

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1) MTD was defined as the highest dose that caused DLT in ≤1 of 6 patients.

2) In patients receiving ≥1 type of chemotherapy, disease progression after achieving CR or CRu by the most recent therapy was defined as "relapsed," and disease progression after achieving PR or SD by the most recent treatment was defined as "flare."

3) Patients with a diagnosis of acute type ATLL, lymphoma-type ATLL, or chronic type ATLL with a poor prognostic factor

Table 4 shows efficacy analysis results, namely, the best overall response and response (complete response [CR], complete response unconfirmed [CRu], or partial response [PR]) rates according to the criteria of the Efficacy Safety Evaluation Committee (ESEC)[4)] partially modified from the criteria proposed by the International Conference on Human Retrovirology (*J Clin Oncol*. 2009;27:453-9). The response rate, the primary endpoint, was significantly higher than the pre-defined threshold response rate (5%[5)]) (one-side significance level of 0.05, $P < 0.0001$ by exact test). Median duration [95% confidence interval (CI)] (weeks) of the efficacy was NE (not evaluated) [2.00, NE].[6)]

Table 4. Best overall response and response rate
(ESEC assessment, efficacy analysis population, data cut-off November 20, 2014)

Best overall response	Number of patients (%) N = 26
CR	4 (15.4)
CRu	1 (3.8)
PR	6 (23.1)
Stable disease (SD)	8 (30.8)
Progressive disease (PD)	7 (26.9)
Response (CR, CRu, or PR) (response rate [95% CI] [%])	11 (42.3 [23.35, 63.08])
P value (one-sided)*	<0.0001

* One-side significance level of 0.05, exact test

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the following review, PMDA has concluded that lenalidomide is expected to be effective in patients with relapsed or recrudescent ATLL.

7.R.1.1 Primary endpoint and efficacy evaluation

In Study ATLL-002, the response rate was the primary endpoint [see Section "7.1.2 Japanese phase II study"].

The applicant's explanation about the rationale for the primary endpoint and the efficacy of lenalidomide:

Responding to the therapy means a success in reducing tumor volume, which is expected to improve accompanying symptoms and delay time to the next treatment, etc. In patients with relapsed or recrudescent ATLL, for which there is no established standard treatment, responding to the therapy per se is clinically significant. Therefore, response rate was selected as the primary endpoint of Study ATLL-002. For the purpose to define clear assessment criteria for non-target lesion and skin lesion, the new assessment criteria were established by partial modification of the criteria proposed by the International Conference on Human Retrovirology (Criteria of International Conference on Human Retrovirology)

4) Efficacy assessment criteria partially modified from the criteria of International Conference on Human Retrovirology

Overall response	Sum of the products of the greatest diameters of target lesion	Non-target lesion		Hepatomegaly, splenomegaly	Skin lesion (PGA)*1	Peripheral blood image	Bone marrow tumour cell infiltration	New lesion
		Nodal	Extranodal					
CR	Normal	Normal	Disappeared	Disappeared	Grade 0	Normal	Negative	Not found
CRu	Reduced by ≥75%	Normal	Disappeared	Disappeared	Grade 0	Normal	Negative	Not found
PR	Reduced by ≥50%	Normal or no increase	Disappeared or no increase	Disappeared or no aggravation	Grade 1, 2, 3	Decreased by ≥50%	Irrelevant or untested	Not found
SD	Reduced by <50% or increased by <50%	Normal or no increase	Disappeared or no increase	Disappeared or no aggravation	Grade 4, 5	Unchanged	Unchanged	Not found
RD/PD*2	Increased by ≥50%	Increased	Increased	Aggravated	Grade 6	Increased by ≥50%	Positive after negative conversion	Found

*1 Skin lesion was assessed based on both the affected area and the symptoms according to PGA (*J Clin Oncol*. 2001;19:2456-71).

*2 Patients who met any of the criteria after achieving CR or CRu were diagnosed as relapsed disease (RD), and patients who met any of the criteria before achieving CR or CRu were diagnosed as PD.

5) At the time when the study was initiated, there was no established standard therapy for patients with relapsed or recrudescent ATLL. Therefore, the threshold response rate was defined by referring to that used in the clinical study of mogamulizumab which was approved for the indication for relapsed or refractory CCR4-positive ATLL *(J Clin Oncol*. 2012;30:837-42).

6) The duration of efficacy ranged from 0.1 to 72.1 weeks.

by referring to the criteria established by the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG) (JCOG-LSG Manual for Clinical Researches of Lymphoma/myeloma, version 1, edited by the JCOG-LSG manual for clinical research committee of lymphoma/myeloma [the Japan Foundation for Aging and Health, 2003]) and to the criteria for the assessment of skin lesion based on physician's global assessment (PGA) (*J Clin Oncol*. 2001;19:2456-71). The response rate in the best overall response was evaluated according to the modified criteria.

In Study ATLL-002, the best overall response rate [95% CI] (%) was 42.3% [23.35%, 63.08%] (11 of 26 patients), which was statistically significantly higher than the pre-defined threshold response rate (5%) [see Section "7.1.2 Japanese phase II study"]. The analysis of the data from Study ATLL-002 based on the Criteria of International Conference on Human Retrovirology could not be performed due to the unavailability of observed data necessary for the analysis based on the Criteria of International Conference on Human Retrovirology.[7)] However, the best overall response rate [95% CI], calculated according to the criteria[8)] adjusted as closely as possible to Criteria of International Conference on Human Retrovirology, was 26.9% [11.57%, 47.79%] (7 of 26 patients). The best overall response rate by disease type, calculated according to the criteria partially modified from Criteria of International Conference on Human Retrovirology, was 33.3% (5 of 15 patients) for acute-type ATLL, 57.1% (4 of 7 patients) for lymphoma-type ATLL, and 50.0% (2 of 4 patients) for chronic type ATLL with a poor prognostic factor.[9)]

PMDA's view:
There is no established standard therapy that extends the survival of patients with relapsed or recrudescent ATLL. The applicant's explanation about on the clinical significance of response to lenalidomide in Study ATLL-002 is thus acceptable. Taking account of the observation that there were responders to lenalidomide in the analysis performed according to the criteria adjusted as closely as possible to Criteria of International Conference on Human Retrovirology, lenalidomide is expected to have efficacy in patients with relapsed or recrudescent ATLL, as judged from the results of Study ATLL-002. Data on the efficacy by disease type should be appropriately provided to healthcare professionals using written materials.

7.R.2 Safety [for adverse events, see Section "7.2 Adverse events observed in clinical studies"]
Based on the discussions in the following subsections, PMDA concluded that lenalidomide therapy in patients with ATLL requires particular attention to the adverse events that were identified in the review of lenalidomide indicated for MM and myelodysplastic syndromes (MDS) (bone marrow depression, venous thromboembolism, neuropathy peripheral, interstitial lung disease, cardiac disorders, hypothyroidism, allergy/hypersensitivity, events associated with delayed wound healing and suppressed angiogenesis, tumour lysis syndrome, cataract, secondary malignancies, infection, haemorrhage, arterial thromboembolism, liver disorder, renal failure, gastrointestinal perforation, orthostatic hypotension, convulsion, and somnolence/confusion/fatigue/dizziness/vision blurred) (see "Review Report on Revlimid Capsules 2.5 mg, 5 mg, dated November 19, 2015").

PMDA also concluded that lenalidomide is well tolerated in patients with ATLL as well where appropriate follow-up, such as monitoring and controlling of adverse events, is performed by a physician with adequate knowledge and experience in the treatment of hematopoietic malignancy.

7.R.2.1 Safety profile of lenalidomide and the difference in safety among patients with different diseases
The applicant's explanation about the safety profile of lenalidomide in patients with ATLL based on the results of Study ATLL-002:
Table 5 shows the outline of the safety of lenalidomide in Study ATLL-002.

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7) According to the Criteria of International Conference on Human Retrovirology, patients are judged to have SD or better response when it lasts for ≥4 weeks. In Study ATLL-002, because efficacy was assessed at 8-week intervals, SD or better response lasting for 4 to <8 weeks may not have been assessed appropriately. RD/PD in skin lesion, according to the Criteria of International Conference on Human Retrovirology, was defined as ≥50% aggravation, while it was defined as ≥25% aggravation in Study ATLL-002. As a result, data of ≥50% aggravation were not collected.

8) Among the Criteria of International Conference on Human Retrovirology, the duration of SD or better response required for such assessment was set at ≥8 weeks, and the criterion for RD/PD in skin lesion was set at ≥25% aggravation.

9) Any of blood urea nitrogen increased, lactate dehydrogenase increased, and serum albumin decreased

Table 5. Outline of safety profile (Study ATLL-002)

	Number of patients (%)
	Study ATLL-002 N = 26
All adverse events	26 (100)
Grade ≥3 adverse events	25 (96.2)
Adverse events resulting in death	0
Serious adverse events	9 (34.6)
Adverse events leading to treatment discontinuation	6 (23.1)
Adverse events leading to treatment interruption	16 (61.5)
Adverse events leading to dose reduction	7 (26.9)

Grade ≥3 adverse events observed in >1 patient in Study ATLL-002 were neutropenia in 17 of 26 patients (65.4%), leukopenia and lymphopenia in 10 of 26 patients (38.5%) each, thrombocytopenia in 6 of 26 patients (23.1%), anaemia in 5 of 26 patients (19.2%), hypokalaemia in 3 of 26 patients (11.5%), and rash, neutrophil count decreased, and hypophosphataemia in 2 of 26 patients (7.7%) each. The serious adverse event observed in >1 patient was thrombocytopenia in 2 of 26 patients (7.7%). Adverse events leading to treatment discontinuation in >1 patient were neutropenia and thrombocytopenia in 2 of 26 patients (7.7%) each.

The applicant's explanation about the difference in the safety of lenalidomide according to different diseases:
Based on the results of the Japanese clinical studies on lenalidomide, the incidences of adverse events were compared among patients with different diseases. Table 6 shows the outline of safety in Study ATLL-002 in patients with ATLL, Study CC-5013-MM-025 (Study MM-025) in patients with previously untreated MM, Studies CC-5013-MM-017 and CC-5013-MM-022 (Study MM-017/022) in patients with relapsed or refractory MM, and Study CC-5013-MDS-007 (Study MDS-007) in patients with MDS.

Table 6. Outline of safety profile, classified by disease (Studies ATLL-002, MM-025, MM-017/022, and MDS-007)

	Number of patients (%)			
	ATLL	MM		MDS
	ATLL-002 N = 26	MM-025 N = 26	MM-017/022[*1] N = 31	MDS-007[*2] N = 11
All adverse events	26 (100)	26 (100)	31 (100)	11 (100)
Grade ≥3 adverse events	25 (96.2)	18 (69.2)	28 (90.3)	11 (100)
Adverse events resulting in death	0	0	1 (3.2)	0
Serious adverse events	9 (34.6)	11 (42.3)	15 (48.4)	3 (27.3)
Adverse events leading to treatment discontinuation	6 (23.1)	4 (15.4)	3 (9.7)	0
Adverse events leading to treatment interruption	16 (61.5)	18 (69.2)	19 (61.3)	10 (90.9)
Adverse events leading to dose reduction	7 (26.9)	13 (50.0)	10 (32.3)	9 (81.8)

[*1] Only patients who received lenalidomide at the starting dose of 25 mg, [*2] Data revised after approval for indication for MDS (at the end of the study [studied period August 2007 to August 2010])

Table 7 shows adverse events with a ≥10% higher incidence in Study ATLL-002 than in Study MM-025, MM-017/022, or MDS-007.

Table 7. Adverse events with a ≥10% higher incidence in Study ATLL-002 than in Study MM-025, MM-017/022, or MDS-007

Preferred term (PT) (MedDRA/J ver. 18.1)	Number of patients (%)			
	ATLL	MM		MDS
	ATLL-002 N = 26	MM-025 N = 26	MM-017/022[*1] N = 31	MDS-007[*2] N = 11
Thrombocytopenia	20 (76.9)	6 (23.1)	17 (54.8)	11 (100)
Neutropenia	19 (73.1)	7 (26.9)	25 (80.6)	11 (100)
Lymphopenia	18 (69.2)	4 (15.4)	19 (61.3)	8 (72.7)
Anaemia	14 (53.8)	8 (30.8)	9 (29.0)	0
Leukopenia	13 (50.0)	6 (23.1)	20 (64.5)	10 (90.9)
C-reactive protein increased	11 (42.3)	0	2 (6.5)	0
Hypoalbuminaemia	9 (34.6)	2 (7.7)	4 (12.9)	0
Hypoproteinaemia	9 (34.6)	0	0	0
Hypocalcaemia	8 (30.8)	1 (3.8)	1 (3.2)	0
Hyponatraemia	8 (30.8)	2 (7.7)	2 (6.5)	0
Hypophosphataemia	7 (26.9)	3 (11.5)	4 (12.9)	1 (9.1)
ALT increased	7 (26.9)	2 (7.7)	5 (16.1)	3 (27.3)
AST increased	7 (26.9)	2 (7.7)	4 (12.9)	2 (18.2)
Nausea	7 (26.9)	2 (7.7)	1 (3.2)	0
Hepatic function abnormal	6 (23.1)	3 (11.5)	7 (22.6)	1 (9.1)
Vomiting	6 (23.1)	2 (7.7)	2 (6.5)	1 (9.1)
Hypokalaemia	6 (23.1)	1 (3.8)	4 (12.9)	0
Malaise	5 (19.2)	4 (15.4)	9 (29.0)	0
Pruritus	5 (19.2)	3 (11.5)	2 (6.5)	5 (45.5)
Leukocytosis	5 (19.2)	0	2 (6.5)	1 (9.1)
Blood alkaline phosphatase increased	5 (19.2)	1 (3.8)	1 (3.2)	1 (9.1)
Blood urea increased	5 (19.2)	2 (7.7)	1 (3.2)	0
Fatigue	4 (15.4)	1 (3.8)	2 (6.5)	0
Hyperkalaemia	4 (15.4)	1 (3.8)	0	0
Neuropathy peripheral	4 (15.4)	0	0	0
Dysgeusia	3 (11.5)	4 (15.4)	7 (22.6)	0
Stomatitis	3 (11.5)	3 (11.5)	4 (12.9)	0
Eosinophilia	3 (11.5)	0	1 (3.2)	5 (45.5)
Basophilia	3 (11.5)	0	0	4 (36.4)
Rash maculo-papular	3 (11.5)	3 (11.5)	0	0
Glucose urine present	3 (11.5)	1 (3.8)	2 (6.5)	0
Hyperchloraemia	3 (11.5)	0	0	0
Hypouricaemia	3 (11.5)	0	0	0
Differential white blood cell count abnormal	3 (11.5)	0	0	0
Tumour flare	3 (11.5)	0	0	0

[*1] Only patients who received lenalidomide at the starting dose of 25 mg, [*2] Data revised after approval for indication for MDS (at the end of the study [studied period August 2007 to August 2010])

Grade ≥3 adverse events with a ≥5% higher incidence in Study ATLL-002 than in Study MM-025, MM-017/022, or MDS-007 were neutropenia (17 of 26 patients [65.4%] in Study ATLL-002, 6 of 26 patients [23.1%] in Study MM-025, 19 of 31 patients [61.3%] in Study MM-017/022, 11 of 11 patients [100%] in Study MDS-007), leukopenia (10 of 26 patients [38.5%], 3 of 26 patients [11.5%], 9 of 31 patients [29.0%], 6 of 11 patients [54.5%]), lymphopenia (10 of 26 patients [38.5%], 3 of 26 patients [11.5%], 9 of 31 patients [29.0%], 5 of 11 patients [45.5%]), thrombocytopenia (6 of 26 patients [23.1%], 4 of 26 patients [15.4%], 3 of 31 patients [9.7%], 5 of 11 patients [45.5%]), anaemia (5 of 26 patients [19.2%], 5 of 26 patients [19.2%], 4 of 31 patients [12.9%], 0 patients), hypokalaemia (3 of 26 patients [11.5%], 0 patients, 0 patients, 0 patients), rash (2 of 26 patients [7.7%], 3 of 26 patients [11.5%], 2 of 31 patients [6.5%], 0 patients), hypophosphataemia (2 of 26 patients [7.7%], 2 of 26 patients [7.7%], 4 of 31 patients [12.9%], 0 patients), and neutrophil count decreased (2 of 26 patients [7.7%], 0 patients, 0 patients, 0 patients). The serious adverse event with a ≥5% higher incidence in Study ATLL-002 than in Study MM-025, MM-017/022, or MDS-007 was thrombocytopenia (2 of 26 patients [7.7%], 1 of 26 patients [3.8%], 0 patients, 0 patients). Adverse events leading to treatment discontinuation with a ≥5% higher incidence in Study ATLL-002 than in Study MM-025, MM-017/022, or MDS-007 were neutropenia (2 of 26 patients [7.7%], 0 patients, 0 patients, 0 patients) and thrombocytopenia (2 of 26 patients [7.7%], 0 patients, 0 patients, 0 patients). Adverse events with an incidence of ≥10% in Study ATLL-002, except tumour flare, hypouricaemia, and differential white blood cell count abnormal, were the same as those

observed in the Japanese and foreign clinical studies[10] in patients with MM or MDS.

PMDA's view:
Caution should be exercised against adverse events such as neutropenia and thrombocytopenia that occurred at a higher incidence in patients with ATLL in Study ATLL-002 than in Study MM-025, MM-017/022, or MDS-007, and appropriate advice should be given to healthcare professionals using written materials. However, in light of the following observations, lenalidomide is considered well tolerated in patients with ATLL where appropriate follow-up, such as monitoring and controlling of adverse events, is performed by a physician with adequate knowledge and experience in the treatment of hematopoietic malignancy:

- The incidence of serious adverse events did not tend to be higher in Study ATLL-002 than in Study MM-025, MM-017/022, or MDS-007.
- Most of the events observed in Study ATLL-002 were also observed in Studies MM-025, MM-017/022, and MDS-007.
- Tumour flare, hypouricaemia, and differential white blood cell count abnormal occurred at an incidence of ≥10% in the Japanese and foreign clinical studies[11] in patients with ATLL but did not occur in the clinical studies in patients with MM or MDS. All of them were Grade 1 or 2 events and did not lead to treatment discontinuation.

In the following subsection, PMDA focuses on tumour flare. Tumour flare is an adverse event observed only in clinical studies on ATLL in the Japanese or foreign clinical studies,[11] and foreign package inserts give a caution against the event.

7.R.2.2 Tumour flare

The applicant's explanation about lenalidomide-induced tumour flare:
The preferred term (PT) of "tumour flare" in the Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) were tabulated.

In Study ATLL-001, tumour flare was observed in 3 of 13 patients (23.1%; 2 of 9 patients (22.2%) with ATLL, 1 of 4 patients (25.0%) with PTCL), and was non-serious events of Grade 1 or 2 in all affected patients. There was no tumour flare leading to treatment discontinuation.

In Study ATLL-002, tumour flare was observed in 3 of 26 patients (11.5%), which was Grade 1 or 2 in all affected patients. Serious tumour flare was observed in 1 of 26 patients (3.8%), and its causal relationship to lenalidomide could not be ruled out. There was no tumour flare leading to treatment discontinuation.

In Studies ATLL-001 and ATLL-002, all tumour flares occurred within 1 month after the start of lenalidomide administration. All patients who had tumour flare in Study ATLL-001 or Study ATLL-002 could continue receiving lenalidomide without dose reduction with the help of an analgesic agent, etc.

The safety database including the post-marketing data (data cut-off [redacted], 20[redacted]) revealed fatal tumour flare in 4 patients. A causal relationship of the fatal tumour flare to lenalidomide could not be ruled out in 3 patients and was not reported in 1 patient. Serious tumour flare was observed in 203 patients. A causal relationship to lenalidomide could not be ruled out for the event in 128 patients and was unknown or not reported in 71 patients. The breakdown of the primary disease in patients who had serious tumour flare was leukaemia in 127 patients (including 3 fatal cases),[12] malignant lymphoma in 56 patients (including 1 fatal case),[13] MM in 5 patients, MDS in 1 patients, and other in 14 patients.[14]

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[10] Japanese clinical studies in patients with MM (Studies MM-025 and MM-017/022), Japanese clinical study in patients with MDS (Study MDS-007), foreign clinical studies in patients with MM (Studies CC-5013-MM-009, CC-5013-MM-010, and CC-5013-MM-020), and foreign clinical studies in patients with MDS (Studies CC-5013-MDS-003 and CC-5013-MDS-004)

[11] Japanese clinical studies in patients with ATLL (Studies ATLL-001 and ATLL-002), Japanese clinical studies in patients with MM (Studies MM-025 and MM-017/022), Japanese clinical study in patients with MDS (Study MDS-007), foreign clinical studies in patients with MM (Studies CC-5013-MM-009, CC-5013-MM-010, and CC-5013-MM-020), and foreign clinical studies in patients with MDS (Studies CC-5013-MDS-003 and CC-5013-MDS-004)

[12] 118 patients with chronic lymphocytic leukaemia, 8 patients with B-cell chronic lymphocytic leukaemia, 1 patient with lymphocytic leukaemia

[13] 17 patients with mantle cell lymphoma, 9 patients with follicular lymphoma, 4 patients with diffuse large B-cell lymphoma, 4 patients with Hodgkin's lymphoma, and 22 patients with other diseases

[14] Mixed lymphosarcoma, relapsed myeloid sarcoma, unknown, etc.

The US package insert gives caution against lenalidomide-induced tumour flare based on the results of clinical studies on chronic lymphocytic leukaemia and clinical studies on mantle cell lymphoma.[15)]

PMDA's view:
All patients who had tumor flare in Study ATLL-001 or Study ATLL-002 could continue receiving lenalidomide without dose reduction with the help of an analgesic agent, etc. In light of this observation, lenalidomide-induced tumour flare is well tolerated in patients with ATLL. However, because patients with ATLL are likely to have a high risk of tumour flare compared with patients with MM or MDS [see Section "7.R.2.1 Safety profile of lenalidomide and the difference in safety among patients with different diseases"], information on the occurrence of tumour flare in the clinical studies should be provided to healthcare professionals using materials. Keeping attention to the onset of tumour flare, new findings, when available, should be appropriately communicated to healthcare professionals.

7.R.3 Clinical positioning and indications

The originally proposed indication for lenalidomide was "relapsed or recrudescent adult T cell leukemia-lymphoma." After the application, it was changed to "relapsed or refractory adult T cell leukemia-lymphoma" by the applicant.

The applicant explained that the following cautionary advice will be given in the "Precautions for Indications" section:

- Eligible patients should be selected based on a good understanding of the study results in the "Clinical Studies" section of the package insert, including the efficacy and safety of lenalidomide.

Based on the discussions in Sections "7.R.1 Efficacy" and "7.R.2 Safety" and in the following subsections, PMDA concluded that the applicant's proposal for the modified indication of lenalidomide, "relapsed or refractory adult T cell leukemia-lymphoma," is appropriate. PMDA also concluded that the "Clinical Studies" section of the package insert should mention the disease types of patients enrolled in Study ATLL-002 and the presence or absence of a poor prognostic factor in these patients, along with the following caution given in the "Precautions for Indications" section:

- Eligible patients should be selected based on a good understanding of the study results in the "Clinical Studies" section of the package insert, including the disease types of patients enrolled in the clinical studies and presence or absence of a poor prognostic factor in these patients, and the efficacy and safety of lenalidomide.

7.R.3.1 Clinical positioning and indications of lenalidomide

Descriptions of lenalidomide for the treatment of relapsed or refractory ATLL in the Japanese and foreign clinical practice guidelines and in the representative textbooks of clinical oncology and hematology are shown below. Currently, there are no descriptions of lenalidomide in the treatment of relapsed or refractory ATLL in Clinical Practice Guidelines for Hematologic Malignancy 2013, edited by Japanese Society of Hematology (Japanese clinical practice guidelines), National Cancer Institute Physician Data Query (NCI-PDQ), or in the representative textbook of clinical oncology or hematology.[16)]

Clinical practice guidelines
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas (NCCN Guideline) (v.3.2016): Lenalidomide monotherapy is one of the treatment options for patients with acute or lymphoma-type, relapsed or refractory ATLL.[17)]

The applicant's explanation about the clinical positioning of lenalidomide for treatment of ATLL and indication:

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15) In the foreign phase II study (Study CC-5013-MCL-001) in patients with mantle cell lymphoma, tumour flare was observed in 13 of 134 patients (9.7%).

16) *New Clinical Oncology*. fourth edition, edited by Japanese Society of Medical Oncology (Nankodo Co., Ltd., 2015), *Wintrobe's Clinical Hematology*. Thirteenth Edition (USA, Lippincott Williams & Wilkins, 2014), *Williams Hematology*. Ninth Edition (USA, The McGraw-Hill Company, Inc., 2016), and *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. Tenth Edition (USA, Lippincott Williams & Wilkins, 2014)

17) It is stated that the second-line therapies used for patients with PTCL are useful as treatment options for patients with acute or lymphoma type, relapsed or refractory ATLL, and lenalidomide monotherapy is described as one of the second-line therapies for patients with PTCL.

ATLL is classified into 4 types, i.e., acute, lymphoma, chronic, or smoldering ATLL. Acute, lymphoma, and chronic ATLL with a poor prognostic factor require aggressive treatment (the Japanese clinical practice guidelines). Although multidrug chemotherapy is performed as the initial treatment to patients with acute ATLL, lymphoma ATLL, or chronic ATLL with a poor prognostic factor, there is no established standard treatment that prolongs the survival of patients with relapsed or refractory ATLL. Clinical benefits of lenalidomide was demonstrated in Study ATLL-002 in patients with relapsed or recrudescent ATLL, a subgroup of the relapsed or refractory ATLL mentioned above, and lenalidomide is recommended for this patient population. Study ATLL-002 excluded (1) patients with acute, lymphoma, or chronic type ATLL with a poor prognostic factors who did not respond to the most recent previous treatment, (2) patients with smoldering ATLL, and (3) patients with chronic ATLL without a poor prognostic factor. However, the following facts indicate that lenalidomide may be administered to patients with relapsed or refractory ATLL, who were excluded from Study ATLL-002:

- The second-line and subsequent therapies for ATLL are not established separately for patients with or without response to previous treatment.
- The Japanese clinical practice guidelines recommend follow-up without treatment for patients with previously untreated smoldering ATLL or chronic ATLL without a poor prognostic factor. However, ATLL of these types evolving to the blast crisis phase is recommended to be treated similarly to acute or lymphoma ATLL or chronic ATLL with a poor prognostic factor. ATLL progressed despite such treatment is also recommended to be treated as with acute or lymphoma ATLL or chronic ATLL with a poor prognostic factor.

Based on the above, recognizing lenalidomide as one of the treatment options for patients with relapsed or refractory ATLL, the applicant proposed to indicate lenalidomide for "relapsed or refractory adult T cell leukemia-lymphoma." Because Study ATLL-002 was initiated almost at the same time when mogamulizumab (genetical recombination) (mogamulizumab) was approved as one of the treatment options for relapsed or refractory ATLL, there are no clinical study data comparing the efficacy and safety of lenalidomide with those of mogamulizumab. However, patients previously treated with mogamulizumab were enrolled in Study ATLL-002. The best overall response rate [95% CI] in patients previously treated with mogamulizumab and in patients not previously treated with mogamulizumab was 18.2% [2.28%, 51.78%] (2 of 11 patients) and 60.0% [32.29%, 83.66%] (9 of 15 patients), respectively.

PMDA's view:
Although Study ATLL-002 began when mogamulizumab was already available as one of the treatment options for relapsed or refractory ATLL, there are no clinical study data comparing the efficacy and safety of lenalidomide with those of mogamulizumab. Therefore, the clinical positioning of lenalidomide relative to mogamulizumab in patients with relapsed or refractory ATLL who are eligible for the treatment with mogamulizumab is unknown. However, the results of Study ATLL-002 demonstrated the clinical benefits of lenalidomide, and lenalidomide is recognized as a treatment option for patient groups enrolled in Study ATLL-002 for the following reasons:

- In Study ATLL-002, some patients previously treated with mogamulizumab responded to lenalidomide.
- Patients with relapsed or refractory ATLL who are CC chemokine receptor 4 (CCR4)-negative are ineligible for treatment with mogamulizumab.

It should be noted that neither the efficacy nor the safety of lenalidomide is known in patients with relapsed or refractory ATLL who are ineligible for Study ATLL-002. Therefore, lenalidomide is not recommended for these patients.

Based on the above understanding, and the premise that lenalidomide is used by physicians with adequate knowledge and experience in chemotherapy of hematopoietic malignancy, patients to be treated with lenalidomide will be selected appropriately where accurate data of clinical study participants are provided to healthcare professionals. Therefore, it is acceptable to indicate lenalidomide for "relapsed or refractory adult T cell leukemia-lymphoma" provided that the disease types of patients enrolled in the clinical studies and the presence or absence of a poor prognostic factor in these patients

are mentioned in the "Clinical Studies" section, along with the following cautionary advice given in the "Precautions for Indications" section of the package insert.

Precautions for Indications
- Eligible patients should be selected based on a good understanding of the study results in the "Clinical Studies" section of the package insert, including the disease types of patients enrolled in the clinical studies and presence or absence of a poor prognostic factor in these patients, and the efficacy and safety of lenalidomide.

7.R.3.2 Use of lenalidomide in patients with ATLL after allogeneic HSCT

A report suggests a relationship between maintenance treatment with lenalidomide in patients with MM after allogeneic hematopoietic stem cell transplantation (HSCT) and graft versus host disease (GVHD) (*Blood*. 2011;118:2413-9). When human leukocyte antigen (HLA)-matched, related or unrelated donor is available for the patient with ATLL, allogeneic HSCT is performed in clinical practice aiming for long-term survival. Therefore, PMDA asked the applicant to explain the safety of lenalidomide in relapsed or refractory ATLL after allogeneic HSCT.

The applicant's explanation:
Of patients who received lenalidomide by June 26, 2014, 110 patients[18)] with a history of allogeneic HSCT were reported to have developed GVHD. This suggests that the administration of lenalidomide to patients with ATLL after allogeneic HSCT may have an influence on the occurrence of GVHD. However, because patients with a history of allogeneic HSCT were excluded from Studies ATLL-001 and ATLL-002, the safety of lenalidomide in these patients is unknown.

PMDA's view:
PMDA accepted the explanation of the applicant. The fact that patients after allogeneic HSCT were excluded from Studies ATLL-001 and ATLL-002 and that there is no use experience of lenalidomide in these patients should be communicated to healthcare professionals using written materials. At the same time, the safety of lenalidomide in post-marketing use in these patients and relevant knowledge from published literature including nonclinical outcomes should be continuously collected, and new findings, when available, should be appropriately communicated to healthcare professionals.

7.R.4 Dosage and administration

The proposed dosage and administration for lenalidomide was "The usual adult dosage is 25 mg of lenalidomide administered orally once daily. The dose may be reduced according to the condition of the patient." In the present application, the "Precautions for Dosage and Administration" section of the package insert provides (1) rough guidelines for treatment interruption, dose reduction, and treatment discontinuation following a lenalidomide-induced adverse event in patients with relapsed or refractory ATLL and highlights (2) that the efficacy and safety in concomitant use with other antineoplastic agents have not been established in patients with relapsed or refractory ATLL.

Based on the discussions in the subsections below and in Sections "7.R.1 Efficacy" and "7.R.2 Safety," PMDA concluded that the dosage and administration of lenalidomide should be specified as proposed by the applicant. Also, the following cautionary advice should be given in the "Precautions for Dosage and Administration" section of the package insert for patients with relapsed or refractory ATLL:
- The interruption, etc. of lenalidomide treatment should be considered by referring to the following table when a decrease in platelet count or neutrophil count is observed.

[18)] The breakdown of the primary disease of patients who had GVHD were MM in 74 patients, leukemia in 24 patients, MDS in 7 patients, and malignant lymphoma in 5 patients.

Guidelines for dose interruption to manage decreased platelet count or neutrophil count in patients with relapsed or refractory adult T cell leukemia-lymphoma

	Platelet count/ neutrophil count	Measures to be taken during treatment and guidelines for dose reduction for treatment resumption
Platelet count decreased	Decreased to <25,000/μL	Interrupt lenalidomide treatment. If platelet count returns to ≥50,000/μL or to baseline level, resume lenalidomide treatment at the following dose: • For platelet count decreased to <10,000/μL or accompanied by haemorrhage requiring platelet transfusion, the dose 1 level* lower than that before the interruption • For other than the above, the same dose as that before the interruption
Neutrophil count decreased	Decreased to <500/μL	Interrupt lenalidomide treatment. If neutrophil count returns to ≥1000/μL or to baseline level, resume lenalidomide treatment at the following dose: • For febrile neutropenia (decrease in neutrophil count to <500/μL accompanied by pyrexia with body temperature of ≥38.5°C lasting for ≥5 days despite treatment with appropriate antibiotics), the dose 1 level* lower than that before the interruption • For other than the above, the same dose as that before the interruption

***Dose level for the resumption of lenalidomide treatment**

Dose level	Dosage and administration of lenalidomide
Starting dose	Oral dose of 25 mg once daily
Dose level 1	Oral dose of 20 mg once daily
Dose level 2	Oral dose of 15 mg once daily
Dose level 3	Oral dose of 10 mg once daily

- The efficacy and safety of lenalidomide in combination with other antineoplastic agents have not been established in patients with relapsed or refractory ATLL.

7.R.4.1 Setting of dosage and administration of lenalidomide

The applicant's rationale for the dosage regimen of lenalidomide for patients with relapsed or refractory ATLL:

In Study ATLL-001 in patients with previously treated ATLL or PTCL, MTD was determined to be daily dose of lenalidomide 25 mg QD [see Section "7.1.1 Japanese phase I study"]. Therefore, in Study ATLL-002, lenalidomide (25 mg) was administered QD without any withdrawal period. The clinical benefits of lenalidomide in patients with relapsed or refractory ATLL was demonstrated in the study. The dosage and administration of lenalidomide was specified based on the dosage regimen used in Study ATLL-002.

PMDA accepted the explanation of the applicant.

7.R.4.2 Adjustment of lenalidomide dose

The applicant's rationale for the criteria for dose adjustment of lenalidomide in patients with relapsed or refractory ATLL:

In Study ATLL-002, criteria for the interruption, reduction, and discontinuation of lenalidomide were used after the onset of lenalidomide-induced adverse events.[19)] Lenalidomide was well tolerated. Therefore, based on the mentioned criteria used in Study ATLL-002, guidelines for dose adjustment in case of lenalidomide-induced thrombocytopenia or neutropenia will be advised in the "Precautions for Dosage and Administration" section of the package insert. For the management of adverse events other than thrombocytopenia and neutropenia, the following advice will be given in the "Precautions for Dosage and Administration" section as is the case with approved indications: (1) In case of Grade 3 or 4 adverse events, interruption or discontinuation of lenalidomide should be considered, and (2) the decision of when to resume lenalidomide administration should be made according to the condition of the patient.

PMDA's view:

[19)] Grade 4 haematologic toxicity (excluding lymphocyte count decreased) or non-haematologic toxicity (persisting Grade ≥3 nausea/vomiting or diarrhoea despite appropriate treatment, Grade 3 AST or ALT persisting for 7 days or Grade 4 AST or ALT, other unacceptable Grade ≥3 non-haematologic toxicity)

PMDA generally accepted the explanation of the applicant. The dose adjustment rules used in Study ATLL-002 should be communicated appropriately to healthcare professionals using written materials, etc.

7.R.4.3 Concomitant use with other antineoplastic agents

The applicant's explanation about the concomitant use of lenalidomide with other antineoplastic agents in patients with relapsed or refractory ATLL:
There are no clinical study data on the efficacy or safety in the concomitant use of lenalidomide with other antineoplastic agents in patients with relapsed or refractory ATLL. Therefore, currently, the lenalidomide is not recommended to be used with other antineoplastic agents for patients with relapsed or refractory ATLL. The following caution should be noted in the "Precautions for Dosage and Administration" section of the package insert: The efficacy and safety of lenalidomide in concomitant use with other antineoplastic agents has not been established.

PMDA accepted the explanation of the applicant.

7.R.5 Post-marketing investigations

The applicant's explanation about their post-marketing surveillance plan:
In order to evaluate the safety, etc. of lenalidomide in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance covering all patients with relapsed or refractory ATLL who are treated with lenalidomide.

The key survey items of the post-marketing surveillance are (a) teratogenicity, which is a risk characteristic to lenalidomide, (b) bone marrow depression, which may occur more frequently with the increasing dose per 28 days than for the approved indications, (c) infection, which is associated with bone marrow depression and is likely to be fatal, and (d) tumour flare, which may occur more frequently in patients with ATLL than in patients treated for approved indications.

The planned sample size is 80, based on the expected incidence of tumour flare that is assumed to occur more frequently in patients with ATLL than in the treatment for other approved indications [see Section "7.R.2.1 Safety profile of lenalidomide and the difference in safety among patients with different diseases"]. The incidence of serious tumour flare in Study ATLL-002 was taken into consideration.

The follow-up period is 6 months from the start of lenalidomide treatment. In Studies ATLL-001 and ATLL-002, most of the adverse events occurred within 3 months from the start of lenalidomide treatment, and continued lenalidomide treatment did not increase the incidence of any adverse event. Therefore, a 6-month period suffices to fully elucidate the occurrence of adverse events in post-marketing clinical use.

PMDA's view:
The following observations indicate little need for post-marketing surveillance as all-case surveillance. However, because of the limited number of patients with ATLL investigated in the clinical studies and the scanty safety data in patients with relapsed or refractory ATLL treated with lenalidomide, post-marketing surveillance is necessary to collect safety data. New findings should be communicated to healthcare professionals.

(a) Study ATLL-002 did not reveal any new adverse events that require particular caution in use of lenalidomide in patients with ATLL as compared with those observed in patients treated for the approved indications in Study MM-025, MM-017/022, or MDS-007 [see Section "7.R.2 Safety"].

(b) Results of the post-marketing surveillance on relapsed or refractory MM and MDS, part of the approved indications, are available (the number of patients included in the safety analysis, 2911).

For the reason given in (a), there is little need to define key survey items at present, and a general survey on lenalidomide-induced adverse events targeting a certain number of patients with ATLL will suffice. The sample size and the follow-up period should be determined so that a comparison of the incidence of adverse events between the survey and Study ATLL-002 is possible.

7.R.6 Proper management procedures

In order to prevent fetal exposure to lenalidomide, the applicant plans to continue with a controlled distribution program (the procedures for proper management of Revlimid and Pomalyst [RevMate]) to enter and manage data of all patients receiving lenalidomide to have patient information including pregnancy available.

PMDA's view:
In using lenalidomide for the treatment of ATLL, as is the case with the use for the approved indications, post-marketing safety management should be conducted according to a strictly controlled distribution program to prevent fetal exposure to lenalidomide.

The appropriateness of the mentioned program in the use of lenalidomide for ATLL is currently under separate review at the Ministry of Health, Labour and Welfare.

7.2 Adverse events observed in clinical studies

The following subsections summarize major adverse events identified in the clinical data submitted for safety evaluation, except death described in Section "7.1 Evaluation data."

7.2.1 Japanese phase I study (Study ATLL-001)

Adverse events were observed in all 13 patients. All patients experienced adverse events for which a causal relationship to lenalidomide could not be ruled out. Table 8 shows adverse events with an incidence of ≥40% in any cohort.

Table 8. Adverse events with an incidence of ≥40% in any cohort

SOC PT (MedDRA/J ver. 12.0)	Number of patients (%)					
	Cohort 1 N = 3		Cohort 2 N = 6		Cohort 3 N = 4	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	6 (100)	5 (83.3)	4 (100)	4 (100)
Investigations						
ALT increased	3 (100)	2 (66.7)	5 (83.3)	0	3 (75.0)	0
AST increased	3 (100)	2 (66.7)	5 (83.3)	0	3 (75.0)	0
Lymphocyte count decreased	3 (100)	3 (100)	5 (83.3)	2 (33.3)	3 (75.0)	2 (50.0)
Neutrophil count decreased	3 (100)	2 (66.7)	4 (66.7)	3 (50.0)	4 (100)	3 (75.0)
Platelet count decreased	3 (100)	1 (33.3)	4 (66.7)	2 (33.3)	3 (75.0)	1 (25.0)
Blood alkaline phosphatase increased	3 (100)	1 (33.3)	4 (66.7)	1 (16.7)	1 (25.0)	0
C-reactive protein increased	1 (33.3)	0	4 (66.7)	0	3 (75.0)	0
Protein total decreased	2 (66.7)	0	3 (50.0)	0	2 (50.0)	0
White blood cell count decreased	1 (33.3)	1 (33.3)	4 (66.7)	2 (33.3)	2 (50.0)	0
Blood bilirubin increased	3 (100)	1 (33.3)	2 (33.3)	1 (16.7)	1 (25.0)	0
Blood lactate dehydrogenase increased	1 (33.3)	0	2 (33.3)	0	2 (50.0)	0
Gamma-glutamyltransferase increased	1 (33.3)	1 (33.3)	3 (50.0)	0	1 (25.0)	0
Eosinophil count increased	0	0	3 (50.0)	0	1 (25.0)	0
Weight increased	1 (33.3)	0	3 (50.0)	0	0	0
Electrocardiogram QT prolonged	0	0	0	0	2 (50.0)	1 (25.0)
Metabolism and nutrition disorders						
Hypoalbuminaemia	3 (100)	0	3 (50.0)	0	2 (50.0)	0
Hypophosphataemia	1 (33.3)	1 (33.3)	4 (66.7)	1 (16.7)	3 (75.0)	1 (25.0)
Hypokalaemia	1 (33.3)	0	2 (33.3)	0	2 (50.0)	1 (25.0)
Hyponatraemia	2 (66.7)	1 (33.3)	1 (16.7)	0	2 (50.0)	0
Inappetence	2 (66.7)	0	1 (16.7)	0	1 (25.0)	1 (25.0)
Skin and subcutaneous tissue disorders						
Rash maculo-papular	2 (66.7)	1 (33.3)	5 (83.3)	0	2 (50.0)	2 (50.0)
Dry skin	2 (66.7)	0	1 (16.7)	0	1 (25.0)	0
Gastrointestinal disorders						
Diarrhoea	1 (33.3)	0	3 (50.0)	0	1 (25.0)	0
Stomatitis	0	0	2 (33.3)	1 (16.7)	3 (75.0)	0
Constipation	0	0	1 (16.7)	0	2 (50.0)	0
Nausea	2 (66.7)	0	0	0	1 (25.0)	0
Blood and lymphatic system disorders						
Anaemia	3 (100)	2 (66.7)	4 (66.7)	1 (16.7)	3 (75.0)	0
Eosinophilia	0	0	1 (16.7)	0	2 (50.0)	0
General disorders and administration site conditions						
Fatigue	2 (66.7)	0	3 (50.0)	0	2 (50.0)	1 (25.0)
Pyrexia	1 (33.3)	0	1 (16.7)	0	2 (50.0)	0
Musculoskeletal and connective tissue disorders						
Back pain	2 (66.7)	0	2 (33.3)	0	0	0
Muscle spasms	2 (66.7)	0	1 (16.7)	0	1 (25.0)	0
Renal and urinary disorders						
Haematuria	0	0	2 (33.3)	0	2 (50.0)	0
Chromaturia	2 (66.7)	0	0	0	0	0
Cardiac disorders						
Sinus tachycardia	1 (33.3)	0	1 (16.7)	0	2 (50.0)	0
Injury, poisoning and procedural complications						
Procedural pain	0	0	0	0	2 (50.0)	0

Serious adverse events occurred in 2 of 3 patients (66.7%) in Cohort 1, 3 of 6 patients (50.0%) in Cohort 2, and 3 of 4 patients (75.0%) in Cohort 3. These events were, namely, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood creatinine increased, pyrexia, and spinal compression fracture in 1 of 3 patients (33.3%) each in Cohort 1; platelet count decreased in 2 of 6 patients (33.3%), white blood cell count decreased, disseminated intravascular coagulation, haemorrhage intracranial, and dermatitis exfoliative in 1 of 6 patients (16.7%) each in Cohort 2; and platelet count decreased, electrocardiogram QT prolonged, neutrophil count decreased, fatigue, herpes zoster, sepsis, and adult T-cell lymphoma/leukaemia in 1 of 4 patients (25.0%) each in Cohort 3. A causal relationship to lenalidomide could not be ruled out for blood creatinine increased and spinal compression

fracture in 1 patient each in Cohort 1; platelet count decreased and dermatitis exfoliative in 1 patient each in Cohort 2; and platelet count decreased, electrocardiogram QT prolonged, neutrophil count decreased, herpes zoster, sepsis, and fatigue in 1 patient each in Cohort 3.

Adverse events led to discontinuation of lenalidomide in none of the patients in Cohort 1, 2 of 6 patients (33.3%) in Cohort 2, and 2 of 4 patients (50.0%) in Cohort 3. These were namely platelet count decreased and haemorrhage intracranial in 1 of 6 patients (16.7%) each in Cohort 2, and electrocardiogram QT prolonged and fatigue in 1 of 4 patients (25.0%) each in Cohort 3. A causal relationship to lenalidomide could not be ruled out for all events except haemorrhage intracranial in 1 patient in Cohort 2.

7.2.2 Japanese phase II study (Study ATLL-002)

Adverse events occurred in all 26 patients. All patients experienced adverse events for which a causal relationship to lenalidomide could not be ruled out. Table 9 shows adverse events with an incidence of ≥20%.

Table 9. Adverse events with an incidence of ≥20%

SOC PT (MedDRA/J ver. 18.1)	Number of patients (%) N = 26	
	All Grades	Grade ≥3
All adverse events	26 (100)	25 (96.2)
Blood and lymphatic system disorders		
Thrombocytopenia	20 (76.9)	6 (23.1)
Neutropenia	19 (73.1)	17 (65.4)
Lymphopenia	18 (69.2)	10 (38.5)
Anaemia	14 (53.8)	5 (19.2)
Leukopenia	13 (50.0)	10 (38.5)
Metabolism and nutrition disorders		
Hypoalbuminaemia	9 (34.6)	0
Hypoproteinaemia	9 (34.6)	0
Hypocalcaemia	8 (30.8)	0
Hyponatraemia	8 (30.8)	1 (3.8)
Hypophosphataemia	7 (26.9)	2 (7.7)
Hypokalaemia	6 (23.1)	3 (11.5)
Investigations		
C-reactive protein increased	11 (42.3)	0
ALT increased	7 (26.9)	1 (3.8)
AST increased	7 (26.9)	0
Skin and subcutaneous tissue disorders		
Rash	6 (23.1)	2 (7.7)
Gastrointestinal disorders		
Constipation	8 (30.8)	0
Nausea	7 (26.9)	0
Vomiting	6 (23.1)	0
Hepatobiliary disorders		
Hepatic function abnormal	6 (23.1)	0

Serious adverse events occurred in 9 of 26 patients (34.6%). These events were, namely, thrombocytopenia in 2 patients (7.7%) and erythema multiforme, rash, toxic skin eruption, anaemia, non-cardiac chest pain, pyrexia, enterocolitis infectious, meningitis bacterial, pneumonia, syncope, transient ischaemic attack, acute left ventricular failure, vertigo positional, acute hepatic failure, blood pressure decreased, tumour flare, acute kidney injury, and pulmonary oedema in 1 patient (3.8%) each. A causal relationship to lenalidomide could not be ruled out for the events except non-cardiac chest pain, syncope, and vertigo positional in 1 patient each.

Adverse events leading to discontinuation of lenalidomide occurred in 6 of 26 patients (23.1%), which were neutropenia and thrombocytopenia in 2 patients (7.7%) each, rash, toxic skin eruption, and acute hepatic failure in 1 patient (3.8%) each. A causal relationship to lenalidomide could not be ruled out for all events.

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 assessment is currently underway. Results and PMDA's conclusion will be reported in the Review Report (2).

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

The assessment is currently underway. Results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that lenalidomide has efficacy in the treatment of relapsed or refractory ATLL and that lenalidomide has acceptable safety in view of its benefits. Lenalidomide is clinically significant because it offers a new treatment option for patients with relapsed or refractory ATLL. The post-marketing investigation items should be discussed further.

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

Review Report (2)

January 13, 2017

Product Submitted for Approval

Brand Name	Revlimid Capsules 2.5 mg, Revlimid Capsules 5 mg
Non-proprietary Name	Lenalidomide Hydrate
Applicant	Celgene K.K.
Date of Application	June 24, 2016

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 in the following. 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 reviewed in Section "7.R.1 Efficacy" of the Review Report (1), the Japanese phase II study (Study CC-5013-ATLL-002 [Study ATLL-002]) on lenalidomide hydrate (to be referred to as lenalidomide) in patients with relapsed or recrudescent adult T cell leukemia-lymphoma (ATLL) yielded the best overall response rate [95% CI], the primary endpoint, of 42.3% [23.35%, 63.08%] (11 of 26 patients). PMDA concluded that lenalidomide is expected to show efficacy in this patient population.

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

1.2 Safety

As reviewed in Section "7.R.2 Safety" of the Review Report (1), PMDA concluded that treatment with lenalidomide in patients with ATLL requires particular attention to adverse events, which were identified as attention-requiring events during the previous reviews for lenalidomide for multiple myeloma (MM) and myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality (bone marrow depression, venous thromboembolism, neuropathy peripheral, interstitial lung disease, cardiac disorders, hypothyroidism, allergy/hypersensitivity, events associated with delayed wound healing and suppressed angiogenesis, tumour lysis syndrome, cataract, secondary malignancies, infection, haemorrhage, arterial thromboembolism, liver disorder, renal failure, gastrointestinal perforation, orthostatic hypotension, convulsion, and somnolence/confusion/fatigue/dizziness/vision blurred), and that there are no additional adverse events requiring caution.

PMDA also concluded that lenalidomide is well tolerated in patients with ATLL as well where appropriate follow-up, such as monitoring and controlling of adverse events, is performed by a physician with adequate knowledge and experience in the treatment of hematopoietic malignancy.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- In Study ATLL-002, 6 of 26 patients (23.1%) experienced lenalidomide-induced rash. The event was Grade 3 in 2 of them (7.7%), and some were serious or led to treatment discontinuation. Therefore, caution should be exercised to the onset of rash.

Based on the above, PMDA instructed the applicant to appropriately communicate the occurrence of rash in Study ATLL-002 to healthcare professionals using written materials. The applicant agreed.

1.3 Clinical positioning and indications

After the review in Section "7.R.3 Clinical positioning and indications" of the Review Report (1), PMDA concluded that lenalidomide should be indicated for "relapsed or refractory adult T cell

leukemia-lymphoma," with the following cautionary advice given in the "Precautions for Indications" section.

Precautions for Indications
- Eligible patients should be selected based on a good understanding of the study results in the "Clinical Studies" section of the package insert, including the disease types of patients enrolled in the clinical studies and presence or absence of a poor prognostic factor in these patients, and the efficacy and safety of lenalidomide.

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

Accordingly, PMDA instructed the applicant to define the indication as above and place the above statement in the "Precautions for Indications" section. The applicant agreed.

1.4 Dosage and administration

After the review in Section "7.R.4 Dosage and administration" of the Review Report (1), PMDA concluded that it is appropriate to specify the dosage and administration of lenalidomide as follows: "The usual adult dosage is 25 mg of lenalidomide administered orally once daily. The dose may be reduced according to the condition of the patient," as proposed by the applicant, with the following cautionary advice provided in the "Precautions for Dosage and Administration" section of the package insert.

Precautions for Dosage and Administration
- The interruption, etc. of lenalidomide treatment should be considered by referring to the following table when a decrease in platelet count or neutrophil count is observed.

Guidelines for dose interruption to manage decreased platelet count or neutrophil count in patients with relapsed or refractory adult T cell leukemia-lymphoma

	Platelet count/ neutrophil count	Measures to be taken during treatment and guidelines for dose reduction for treatment resumption
Platelet count decreased	Decreased to <25,000/μL	Interrupt lenalidomide treatment. If platelet count returns to ≥50,000/μL or to baseline level, resume lenalidomide treatment at the following dose: • For platelet count decreased to <10,000/μL or accompanied by haemorrhage requiring platelet transfusion, the dose 1 level* lower than that before the interruption • For other than the above, the same dose as that before the interruption
Neutrophil count decreased	Decreased to <500/μL	Interrupt lenalidomide treatment. If neutrophil count returns to ≥1000/μL or to baseline level, resume lenalidomide treatment at the following dose: • For febrile neutropenia (decrease in neutrophil count to <500/μL accompanied by pyrexia with body temperature of ≥38.5°C lasting for ≥5 days despite treatment with appropriate antibiotics), the dose 1 level* lower than that before the interruption • For other than the above, the same dose as that before the interruption

***Dose level for the resumption of lenalidomide treatment**

Dose level	Dosage and administration of lenalidomide
Starting dose	Oral dose of 25 mg once daily
Dose level 1	Oral dose of 20 mg once daily
Dose level 2	Oral dose of 15 mg once daily
Dose level 3	Oral dose of 10 mg once daily

- The efficacy and safety of lenalidomide in combination with other antineoplastic agents have not been established in patients with relapsed or refractory ATLL.

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

Accordingly, PMDA instructed the applicant to specify the Dosage and Administration and Precautions for Dosage and Administration sections as above. The applicant agreed.

1.5 Risk management plan (draft)

1) Post-marketing surveillance

In order to evaluate the safety, etc. of lenalidomide in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance covering all patients with relapsed or refractory ATLL who are treated with lenalidomide, with the planned sample size of 80 patients and the follow-up period of 6 months.

As reviewed in "7.R.5 Post-marketing investigations" of the Review Report (1), PMDA concluded that, although there is little need of all-case surveillance, post-marketing surveillance must be conducted because of the limited available safety data on treatment with lenalidomide in patients with relapsed or refractory ATLL due to the small number of patients with ATLL investigated in the clinical studies, and that safety findings from the surveillance should be communicated to healthcare professionals.

PMDA further concluded that the surveillance plan should be designed as follows:

- There is little need to define key survey items. A general survey on lenalidomide-induced adverse events targeting a certain number of patients with ATLL will suffice.
- The sample size and the follow-up period should be determined so that a comparison of the incidence of adverse events between the survey and Study ATLL-002 is possible.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- There is only limited data on tumour flare available from the clinical studies. The surveillance should be planned to allow the collection of the relevant data.
- Unlike patients with MM or MDS associated with a deletion 5q abnormality, patients with ATLL are required to receive lenalidomide daily. Because of no withdrawal period given for recovery from lenalidomide-induced bone marrow depression, precautions should be taken against infection.

Based on the above, PMDA instructed the applicant to re-examine the surveillance plan.

The applicant's response:

- The surveillance will be redesigned as non-all-case surveillance. The planned sample size is 80 and the follow-up period is 6 months based on the occurrence of adverse events in Study ATLL-002.
- No key survey item will be defined. However, once the survey identifies the onset of tumour flare or infection, relevant data will be further collected. Based on the findings obtained, the necessity of new cautionary advice will be discussed.

PMDA accepted the response of the applicant.

2) Procedures for proper management

In order to prevent fetal exposure to lenalidomide, the applicant plans to continue with a controlled distribution program (the procedures for proper management of Revlimid and Pomalyst [RevMate]) to enter and manage data of all patients receiving lenalidomide to have patient information including pregnancy available.

As a result of the review in Section "7.R.6 Proper management procedures" of the Review Report (1), PMDA concluded that lenalidomide should be used for the treatment of relapsed or refractory ATLL along with a strictly controlled distribution program aimed to prevent fetal drug exposure, as practiced for the approved indications, to continue post-marketing safety management of lenalidomide.

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

In view of the discussion above, PMDA concluded that the risk management plan (draft) for lenalidomide should include the safety and efficacy specifications presented in Table 10, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 11.

Table 10. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Teratogenicity • Bone marrow depression • Haemorrhage • Infection • Thromboembolism • Hypersensitivity (including skin reaction) • Tumour lysis syndrome • Neuropathy peripheral • Ischaemic heart disease • Cardiac failure • Arrhythmia • Renal failure • Interstitial lung disease • Liver disorder • Hypothyroidism • Gastrointestinal perforation • Orthostatic hypotension • Convulsion • Somnolence, confusion, fatigue, dizziness, vision blurred • Secondary malignancies	• Cataract	• Safety in long-term treatment • Progression from MDS to acute myeloid leukaemia (AML)
Efficacy specification (related to the present application for partial change approval)		
• Efficacy in patients with relapsed or refractory ATLL in routine clinical use		

Table 11. Summary of additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Post-marketing surveillance in patients with ATLL • Post-marketing surveillance in patients with relapsed or refractory MM and patients with MDS associated with a deletion 5q abnormality (all-case surveillance) • Post-marketing surveillance in patients with relapsed or refractory MM (long-term use) • Post-marketing surveillance in patients with MDS associated with a deletion 5q abnormality (progression from MDS to AML) • Post-marketing surveillance in patients with previously untreated MM • Post-marketing clinical study in patients with previously untreated MM (extension of Study CC-5013-MM-025)	• Implementation of the controlled distribution program • Preparation and distribution of information materials for healthcare professionals • Publication of the occurrence of lenalidomide-induced adverse drug reactions on the sponsor's website

Underline denotes activity for the additional indication in the present application.

Table 12. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety, etc. of lenalidomide in post-marketing use
Survey method	Central registration system
Population	Patients with relapsed or refractory ATLL treated with lenalidomide
Follow-up period	6 months
Planned sample size	80
Main survey items	Patient characteristics (sex, age, pregnancy status, medical history, comorbidity, etc.), previous treatment for the primary disease, status of lenalidomide administration, concomitant drugs, adverse events (including changes in laboratory test values), etc.

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

2.1 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

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

The new drug application data (CTD 5.3.5.2.1, CTD 5.3.5.2.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following inadequacies at some medical centers and the sponsor. The findings, despite no significant impact on the overall evaluation of the study, were notified to the head of the pertinent medical centers and the applicant (sponsor) to seek improvement.

Areas for improvement

Medical centers

- Protocol deviation (noncompliance with the rules related to the interruption of the study drug)

Sponsor

- Delay in periodical safety reporting to investigators and the head of medical centers

3. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved for the indication and dosage and administration modified as shown below, with the following conditions, provided that appropriate cautionary advice is given in the package insert and information concerning the proper use of lenalidomide is disseminated appropriately in the post-marketing setting. The proper use of lenalidomide must be observed under the supervision of a physician with adequate knowledge and experience in the treatment of hematopoietic malignancy at a medical institution well-prepared for emergency care. Lenalidomide is designated as an orphan drug with the expected indication of "relapsed or refractory adult T cell leukemia-lymphoma," and thus the re-examination period should be 10 years.

Indications (Underline denotes addition.)

1. Multiple myeloma
2. Myelodysplastic syndromes associated with a deletion 5q abnormality
3. Relapsed or refractory adult T cell leukemia-lymphoma

Dosage and administration (Underline denotes addition.)

1. Multiple myeloma

In combination with dexamethasone, the usual adult dosage is 25 mg of lenalidomide administered orally once daily for 21 days, followed by a 7-day withdrawal period. This treatment cycle is repeated. The dose may be reduced according to the condition of the patient.

2. Myelodysplastic syndromes associated with a deletion 5q abnormality

The usual adult dosage is 10 mg of lenalidomide administered orally once daily for 21 days, followed by a 7-day withdrawal period. This treatment cycle is repeated. The dose may be reduced according to the condition of the patient.

3. Relapsed or refractory adult T cell leukemia-lymphoma

The usual adult dosage is 25 mg of lenalidomide administered orally once daily. The dose may be reduced according to the condition of the patient.

Conditions of approval

1. The applicant is required to comply with "the procedures for proper management of Revlimid and Pomalyst" in the production, control, and use of product. Any modification to the procedures is subject to the pre-approval by the Ministry of Health, Labour and Welfare.

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

3. The applicant is required to ensure by strict and appropriate means that lenalidomide is used only for patients recognized as eligible for the therapy, under the supervision of a knowledgeable and experienced physician at a medical institution well-prepared for emergency care. The benefits and

risks of the product must be explained to the patient or their family member in a written form and written consent must be obtained prior to the therapy.

Warning (No change)

1. Lenalidomide is a thalidomide derivative and may be teratogenic in humans. Lenalidomide should not be administered to pregnant women or women who may possibly be pregnant.

2. To avoid fetal exposure to lenalidomide, the established proper management procedures for the use of lenalidomide must be observed by all parties concerned, i.e., relevant businesses, healthcare providers including physicians and pharmacists, and patients and their family members.

3. Women of childbearing potential should undergo a pregnancy test and are required to be negative for pregnancy before the use of lenalidomide. During the period from 4 weeks before the start of treatment until 4 weeks after the end of treatment, patients of childbearing potential and their partner should be advised to adhere to most effective contraceptive measures (male partners must wear a condom) for sexual intercourse. Patient adherence to contraceptive use must be closely checked, and pregnancy test must be performed regularly. Patients who may have become pregnant during treatment should be instructed to stop using lenalidomide immediately and contact their physician.

4. Lenalidomide is excreted into seminal fluid. Patients and their partner should be advised to adhere to most effective contraceptive measures (male partners must wear a condom) for sexual intercourse during the period from 4 weeks before the start of treatment until 4 weeks after the end of treatment. Patient adherence to contraceptive use must be closely checked. Male patients receiving lenalidomide must not be allowed to have sexual intercourse with a pregnant woman during the above-mentioned period.

5. Lenalidomide should be administered only to patients considered eligible for the therapy by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy at a medical institution well-prepared for emergency care. Patients or their families should be fully informed of the efficacy and risks (including the risk of fetal exposure to lenalidomide) of the treatment. Written consent should be obtained before starting treatment.

6. Deep vein thrombosis and pulmonary embolism have been reported. Patients should be closely monitored and lenalidomide should be administered carefully. If any abnormalities are observed, lenalidomide should be discontinued immediately and appropriate measures should be taken.

Contraindications (No change)

1. Pregnant women or women who may possibly be pregnant
2. Patients who are unable to adhere to the proper management procedures
3. Patients with a history of hypersensitivity to any of the ingredients of lenalidomide

Precautions for Indications (Underline denotes addition.)

1. <u>Patients with multiple myeloma or myelodysplastic syndromes associated with a deletion 5q abnormality</u> to be treated with lenalidomide should be selected based on the good understanding of the "Clinical Studies" section of the package insert, including the efficacy and safety of lenalidomide.

2. For myelodysplastic syndromes associated with a deletion 5q abnormality with intermediate-2 or high risk according to IPSS,[*] neither efficacy nor safety of lenalidomide has been established.

3. <u>Patients with relapsed or refractory adult T cell leukemia-lymphoma to be treated with lenalidomide should be selected based on the good understanding of the "Clinical Studies" section of the package insert, which presents the disease types of patients enrolled in the clinical studies and the presence or absence of a poor prognostic factor in these patients, and of the efficacy and safety of lenalidomide.</u>

[*] International prognostic scoring system

Precautions for Dosage and Administration (Strike-through denotes deletion and underline addition.)

1. In patients with multiple myeloma, cancer chemotherapy including lenalidomide should be performed with the good understanding of the "Clinical Studies" section, dosage and administration in particular.

2. In patients with multiple myeloma, the efficacy and safety of lenalidomide monotherapy have not been established.

3. <u>In patients with relapsed or refractory adult T cell leukemia-lymphoma, the efficacy and safety of lenalidomide in combination with other antineoplastic agents have not been established.</u>

4. Patients with renal impairment are known to show increased blood lenalidomide concentration. The adjustment of dose and dosing interval should be considered, and patients should be carefully monitored for possible adverse events.

5. A dose of lenalidomide following a high-fat diet shows decreased AUC and C_{max}. The administration of lenalidomide before or after a high-fat diet should preferably be avoided.

6. The interruption or discontinuation of lenalidomide treatment should be considered when a Grade 3<u>*</u> or 4<u>*</u> adverse drug reaction <u>(according to CTCAE) other than decreased platelet or neutrophil count</u> ~~(except decreases in platelet or neutrophil count)~~ occurs. A decision on when to resume treatment should be made according to the condition of the patient.

7. The interruption, etc. of lenalidomide treatment should be considered by referring to the following table when a decrease in platelet count or neutrophil count is observed.
   ~~* CTCAE V 3.0~~

Guidelines for dose interruption to manage decreased platelet count or neutrophil count in patients with previously untreated multiple myeloma

	Platelet count/ neutrophil count	Measures to be taken during treatment and guidelines for dose reduction for treatment resumption
Platelet count decreased	Decreased to <25,000/μL	Interrupt lenalidomide treatment. If platelet count returns to ≥50,000/μL, resume lenalidomide treatment at the dose 5 mg less than that before the interruption. If receiving 5 mg once daily before interruption, resume lenalidomide at 2.5 mg once daily.
Neutrophil count decreased	Decreased to <500/μL or febrile neutropenia (<1000/μL with body temperature of ≥38.5°C)	Interrupt lenalidomide treatment. If neutrophil count returns to ≥1000/μL, resume lenalidomide treatment at the dose 5 mg less than the previous dose. If receiving 5 mg once daily before interruption, resume lenalidomide at 2.5 mg once daily.

If bone marrow function resolves after the dose reduction according to the physician's diagnosis, then, the dose may be increased by 5 mg each (or from 2.5 mg to 5 mg). The dose should not exceed the starting dose.

Guidelines for dose interruption to manage decreased platelet count or neutrophil count in patients with relapsed or refractory multiple myeloma

	Platelet count/ neutrophil count	Measures to be taken during treatment and guidelines for dose reduction for treatment resumption
Platelet count decreased	Decreased to <30,000/μL	Interrupt lenalidomide treatment. If platelet count returns to ≥30,000/μL, resume lenalidomide treatment at 15 mg once daily.
	Decreased to <30,000/μL again after the second or later interruption	Interrupt lenalidomide treatment. If platelet count returns to ≥30,000/μL, resume lenalidomide treatment once daily at the dose 5 mg less than the previous dose.
Neutrophil count decreased	Decreased to <1000/μL	Interrupt lenalidomide treatment. 1) If neutrophil count returns to ≥1000/μL (without any adverse drug reaction other than the decreased neutrophil count), resume lenalidomide treatment at 25 mg once daily. 2) If neutrophil count returns to ≥1000/μL (with an adverse drug reaction other than the decreased neutrophil count), resume lenalidomide treatment at 15 mg once daily.
	Decreased to <1000/μL again after the second or later interruption	Interrupt lenalidomide treatment. If neutrophil count returns to ≥1000/μL, resume lenalidomide treatment once daily at the dose 5 mg less than the previous dose.

Guidelines for dose interruption to manage decreased platelet count or neutrophil count in patients with myelodysplastic syndromes associated with a deletion 5q abnormality

	Platelet count/ neutrophil count	Measures to be taken during treatment and guidelines for dose reduction for treatment resumption
Platelet count decreased	Decreased to <25,000/μL	Interrupt lenalidomide treatment. Resume lenalidomide treatment at the dose 1 level* lower than the dose before the interruption if • Platelet count returns to ≥50,000/μL. • Platelet count measured twice or more at ≥7-day intervals is 25,000/μL to 50,000/μL.
Neutrophil count decreased	Decreased to <500/μL	Interrupt lenalidomide treatment. If neutrophil count has increased to ≥500/μL, resume lenalidomide treatment at the dose 1 level* lower than the dose before the interruption.

***Dose level for the resumption of lenalidomide treatment**

Dose level	Dosage and administration of lenalidomide
Starting dose	Oral dose of 10 mg once daily for 21 days, followed by a 7-day withdrawal period. Repeat this treatment cycle.
Dose level 1	Oral dose of 5 mg once daily
Dose level 2	Oral dose of 5 mg once every 2 days
Dose level 3	Oral dose of 5 mg twice a week

Guidelines for dose interruption to manage decreased platelet count or neutrophil count in patients with relapsed or refractory adult T cell leukemia-lymphoma

	Platelet count/ neutrophil count	Measures to be taken during treatment and guidelines for dose reduction for treatment resumption
Platelet count decreased	Decreased to <25,000/μL	Interrupt lenalidomide treatment. If platelet count returns to ≥50,000/μL or to baseline level, resume lenalidomide treatment at the following dose: • For platelet count decreased to <10,000/μL or accompanied by haemorrhage requiring platelet transfusion, the dose 1 level** lower than that before the interruption • For other than the above, the same dose as that before the interruption
Neutrophil count decreased	Decreased to <500/μL	Interrupt lenalidomide treatment. If neutrophil count returned to ≥1000/μL or to baseline level, resume lenalidomide treatment at the following dose: • For febrile neutropenia (decrease in neutrophil count to <500/μL accompanied by pyrexia with body temperature of ≥38.5°C lasting for ≥5 days despite treatment with appropriate antibiotics), the dose 1 level** lower than that before the interruption • For other than the above, the same dose as that before the interruption

[**]Dose level for the resumption of lenalidomide treatment

Dose level	Dosage and administration of lenalidomide
Starting dose	Oral dose of 25 mg once daily
Dose level 1	Oral dose of 20 mg once daily
Dose level 2	Oral dose of 15 mg once daily
Dose level 3	Oral dose of 10 mg once daily