Report on the Deliberation Results

March 10, 2017

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

Brand Name	Mundesine Capsule 100 mg
Non-proprietary Name	Forodesine Hydrochloride (JAN*)
Applicant	Mundipharma K.K.
Date of Application	June 7, 2016

Results of Deliberation

In its meeting held on March 3, 2017, the Second Committee on New Drugs concluded that 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 product is not classified as a biological product or a specified biological product, and the re-examination period of the product is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of patients participated in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data of a certain number of patients are accumulated to identify the characteristics of treated patients and to collect safety and efficacy data early. Based on the data obtained, the applicant should take necessary measures to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

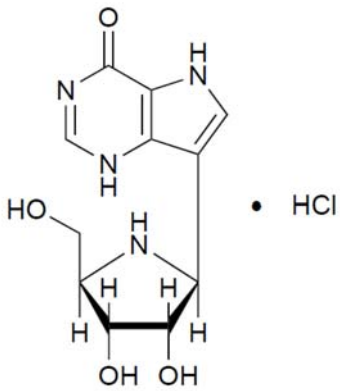
Review Report

February 22, 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 (PMDA).

Brand Name	Mundesine Capsule 100 mg
Non-proprietary Name	Forodesine Hydrochloride
Applicant	Mundipharma K.K.
Date of Application	June 7, 2016
Dosage Form/Strength	Capsules each containing 113.6 mg of forodesine hydrochloride (100 mg of forodesine)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{11}H_{14}N_4O_4 \cdot HCl$

Molecular weight: 302.71

Chemical name: 7-[(2*S*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidin-2-yl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one monohydrochloride

Items Warranting Special Mention

Orphan drug (Drug Designation No. 212 of 2008 [*20 yaku*]; PFSB/ELD Notification No. 0606011 dated June 6, 2008, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety 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 peripheral T-cell 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, dosage and administration as shown below, with the following conditions. Further investigation is expected through post-marketing surveillance on adverse events including hematotoxicity, infections, Epstein-Barr virus-associated malignant lymphoma (including Epstein-Barr virus-associated lymphoproliferative disorders), secondary malignancies other than Epstein-Barr virus-associated malignant lymphoma, peripheral nerve disorder, skin disorder, and cardiac failure.

Indication(s) Relapsed or refractory peripheral T-cell lymphoma

Dosage and Administration

The usual adult dosage is 300 mg of oral forodesine administered twice daily. The dose should be reduced according to the patient's condition.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of patients participated in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data of a certain number of patients are accumulated to identify the characteristics of treated patients and to collect safety and efficacy data early. Based on the data obtained, the applicant should take necessary measures to ensure the proper use of the product.

Attachment

Review Report (1)

December 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.

Product Submitted for Approval	
Brand Name	Mundesine Capsule 100 mg
Non-proprietary Name	Forodesine Hydrochloride
Applicant	Mundipharma K.K.
Date of Application	June 7, 2016
Dosage Form/Strength	Capsules each containing 113.6 mg of forodesine hydrochloride (100 mg of forodesine)
Proposed Indication(s)	Relapsed or refractory peripheral T-cell lymphoma
Proposed Dosage and Administration	The usual adult dosage is 300 mg of oral forodesine administered twice daily. The dose should be reduced according to the patient's condition.

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List of Abbreviations

AITL	angioimmunoblastic T cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
Application	application for marketing approval
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BA	bioavailability
Bendamustine	bendamustine hydrochloride

BID	bis in die
Brentuximab	brentuximab vedotin (genetical recombination)
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CR	complete remission
CrCL	creatinine clearance
CTCL	cutaneous T cell lymphoma
CYP	cytochrome P450
dCK	2′-deoxycytidine kinase
dCyt	2′-deoxycytidine
dGMP	2′-deoxyguanosine monophosphate
dGTP	2′-deoxyguanosine triphosphate
dGuo	2′-deoxyguanosine
DLBCL	diffuse large B cell lymphoma
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DNFB	2,4-dinitorofluorobenzene
dNTP	2′-deoxynucleotide triphosphate
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
efflux ratio	the ratio of the secretory permeability to the absorptive permeability
ESMO Guidelines	Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
GVH	graft-versus-host
GVHD	graft-versus-host disease
HBV	hepatitis B virus
hERG	human *ether-a-go-go* related gene
HPLC	high performance liquid chromatography
IL-2	interleukin-2
IR	infrared spectroscopy
Japanese clinical practice guidelines	the Hematopoietic Tumor Guidelines 2013, edited by the Japanese Society of Hematology (Kanehara Shuppan, 2013)
LC-MS/MS	liquid chromatography-tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mogamulizumab	mogamulizumab (genetical recombination)
MTD	maximum tolerated dose
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NMR	nuclear magnetic resonance spectrum
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
PBL	peripheral blood lymphocyte
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PNP	purine nucleoside phosphorylase
PPK	population pharmacokinetics
PR	partial remission
PS	performance status
PT	preferred term
PTCL	peripheral T-cell lymphoma
PTCL-NOS	peripheral T-cell lymphoma, not otherwise specified

PTP	press through packaging
QD	puaque die
Revised RC	Revised Response Criteria for Malignant Lymphoma
SCID mice	severe combined immunodeficient mice
SD	stable disease
SMQ	standard MedDRA queries
SOC	system organ class
Study J01	Study BCX1777-J01
Study J02	Study FDS-J02
Study 105	Study BCX1777-105
Study 112	Study BCX1777-112
Study 116	Study BCX1777-116
Study 203	Study BCX1777-203
Study 204	Study BCX1777-204
Study 210	Study BCX1777-210
T-ALL	T-cell acute lymphoblastic leukemia
T-ALL/T-LBL	T-acute lymphoblastic leukemia/T-acute lymphoblastic lymphoma
TID	ter in die
T/NK-cell tumors	mature T cell/NK cell tumors
UV/VIS	ultraviolet/visible spectrum
Vc/F	apparent central volume of distribution
WHO	World Health Organization

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

1.1 Summary of product submitted for approval

Purine nucleoside phosphorylase (PNP) catalyzes the phosphorolysis of purine nucleosides such as 2′-deoxyguanosine (dGuo) and deoxyinosine to produce the bases and deoxyribose-1-phosphate. Because patients with PNP deficiency undergo T-cell depletion, PNP is considered essential for T-cell proliferation (*Immunodefic Rev.* 1991;3:45-81).

Forodesine hydrochloride (forodesine) is a low-molecular-weight compound with PNP inhibitory effect developed by BioCryst Pharmaceuticals, Inc. in the US. Forodesine is expected to inhibit PNP, an enzyme essential for T cell proliferation, and increase dGuo accumulation in cells, inducing apoptosis (*Molecules*. 2009;14:1183-226) and thereby inhibiting the proliferation of T cell-derived malignancies.

1.2 Development history

The applicant started a Phase I study (Study BCX1777-J01, referred to as Study J01) in patients with relapsed or refractory mature T cell/NK cell tumors (T/NK-cell tumors) in Japan in January 2009. The applicant also conducted a Phase I/II study (Study FDS-J02, referred to as Study J02) in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) from January 2013.

Outside Japan, no clinical studies have been conducted in patients with PTCL, the target patient population for the proposed indication of the application. As of October 2016, forodesine has not been approved in other countries or regions for the treatment of PTCL or other indications.

Based on the results from the pivotal Study J02, the application for approval of forodesine has now been submitted.

In June 2008, forodesine was designated as an orphan drug (Designation No.: [*20 yaku*] No. 212) for the proposed indication of "relapsed or refractory diseases: peripheral T-cell lymphoma, adult T-cell leukemia/lymphoma, cutaneous T-cell lymphoma, and T-cell acute lymphocytic leukemia/T-cell lymphoblastic leukemia."

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. Its description, solubility, hygroscopicity, melting point, pH, dissociation constant, and partition coefficient were determined. Forodesine hydrochloride is known to exist in 4 different crystalline forms (Forms A, B, B1, and C), and Forms A and B are identified in the drug substance. No clear differences were identified between Forms A and B in terms of dissolution characteristics, stability, and other properties.

The chemical structure of the drug substance was elucidated by elemental analysis, chloride content,

ultraviolet/visible spectrum (UV/VIS), infrared spectroscopy (IR), nuclear magnetic resonance spectrum (^{1}H- and ^{13}C-NMR), mass spectrometry, and powder X-ray diffraction pattern.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted][1)] and [redacted][2)] as the starting materials.

The synthetic processes of [redacted][3)] and [redacted][4)] were defined as critical steps, and process control items and process control values were specified. [redacted] and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (UV/VIS and high performance liquid chromatography [HPLC]), purity (heavy metals, palladium [inductively coupled plasma mass spectrometry], related substances [HPLC], residual solvents [gas chromatography]), water content, residue on ignition, microbial limit testing, chloride content (HPLC), and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows a summary of the stability studies on the drug substance. Photostability testing demonstrated that the drug substance was photostable.

Table 1. Stability studies on the drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	Low-density polyethylene bag + high-density polyethylene container	60 months
Accelerated		40°C	75% RH		6 months

Based on the above, a retest period of [redacted] months was proposed for the drug substance when placed in a low-density polyethylene bag, stored in a high-density polyethylene container at room temperature.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate release hard capsules, each containing 113.6 mg of forodesine hydrochloride (100.0 mg as forodesine). The drug product contains crystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate as excipients.

1) [redacted]
2) [redacted]
3) [redacted]
4) [redacted]

2.2.2 Manufacturing process

The drug product is produced through a manufacturing process comprising [redacted], granulation/[redacted], sizing, packaging, mixing, encapsulation, and packaging/labeling.

[redacted], [redacted], [redacted], and [redacted] have been defined as critical steps, and process control items and process control values have been specified for [redacted] and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product were content, description, identification (UV/VIS and HPLC), purity (related substances [HPLC]), water content, uniformity of dosage units (mass variation test), dissolution (ultraviolet-visible spectrophotometry), and assay (HPLC).

2.2.4 Stability of drug product

Table 2 shows a summary of the stability studies on the drug product. Photostability testing demonstrated that the drug product was photostable.

Table 2. Stability studies on the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	PTP sheet	36 months
Accelerated		40°C	75% RH		6 months

Based on the above, a retest period of 36 months was proposed for the drug product when packed in a press through packaging (PTP, polyvinyl chloride-coated polyvinylidene chloride/aluminum foil) and then in an aluminum pillow bag (polyethylene phthalate/aluminum/polyethylene laminated film) at room temperature. The long-term stability study will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

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

3.1 Primary pharmacodynamics

3.1.1 PNP inhibitory effect (CTD 4.2.1.1.1)

The inhibitory effect of forodesine on human, mouse, rat, dog, or monkey red blood cell PNP was studied using the amount of ^{14}C labeled inosine ([8-^{14}C] inosine) converted to [8-^{14}C] hypoxanthine as an indicator. Table 3 shows the IC_{50} values for the PNPs studied.

Table 3. PNP inhibitory activities of forodesine

Animal species	IC_{50} (nmol/L)
Human	1.19 ± 0.21
Mouse	0.48 ± 0.13
Rat	1.24 ± 0.17
Dog	1.57 ± 0.14
Monkey	0.66 ± 0.04

Mean ± standard error, n = 3 to 4

3.1.2 The dissociation half-life from PNP (CTD 4.2.1.1.2)

To elucidate the binding characteristics of forodesine to PNP, the dissociation half-life (time required for 50% dissociation of forodesine from PNP) was studied with PNP activity as the indicator using a human red blood cell PNP-forodesine complex, which was sampled by equilibrium dialysis. The dissociation half-life was 72 hours (n = 1).

3.1.3 Antiproliferative effects against lymphocytes and malignancies (CTD 4.2.1.1.3, CTD 4.2.1.1.4, CTD 4.2.1.1.5, and CTD 4.2.1.1.8)

- The antiproliferative effect of forodesine against lymphocyte proliferation caused by interleukin-2 (IL-2) or alloantigen stimulation was studied in human peripheral blood lymphocyte (PBL) using ^{3}H-thymidine incorporation into cells as the indicator for both stimulations. In the presence of dGuo, the antiproliferative effect of forodesine was confirmed through both stimulations, with IC_{50} (mean ± standard error) of 0.06 ± 0.02 μmol/L (n = 7) by IL-2 and 0.06 ± 0.03 μmol/L (n = 4) by alloantigen.
- (a) Using human PBL, IL-2 stimulated antiproliferative effect of forodesine against lymphocyte proliferation was studied based on ^{3}H-thymidine incorporation into cells as the indicator. In the presence of dGuo, forodesine inhibited lymphocyte proliferation. (b) Using human PBL, IL-2 stimulated effect of forodesine on cellular 2′-deoxyguanosine triphosphate (dGTP) concentration was studied by polymerase assay. Forodesine increased cellular dGTP concentration. These effects were weakened in the presence of 2′-deoxycytidine (dCyt), which inhibits the catalyzer 2′-deoxycytidine kinase (dCK) that converts dGuo into 2′-deoxyguanosine monophosphate (dGMP) (Table 4). The effects described in (a) and (b) were not observed in similar studies using non-human PBLs, etc.

Table 4. The inhibitory effect of forodesine on lymphocyte proliferation, and effects of forodesine on cellular dGTP concentration

Concentration of forodesine (μmol/L)	dGuo	dCyt	Percent inhibition of proliferation* (%)	Cellular dGTP concentration (pmol/8 × 10^{6} cells)
0 (control)	Absent	Absent	0	3.8 ± 0.5
0.1	Present	Absent	51.7 ± 6.1	17.6 ± 3.6
1	Present	Absent	75.9 ± 3.9	29.1 ± 3.3
1	Present	Present	32.8 ± 11.9	10.8 ± 2.7

Mean ± standard error; n = 4; * percent inhibition of proliferation = {1 − (the proportion of proliferation rate of the forodesine group when the proliferation rate of the control group is taken as 1)} × 100

- In human T-cell acute lymphoblastic leukemia (T-ALL) CEM cell lines, and human cutaneous T cell lymphoma (CTCL) MJ and Hut-78 cell lines, (a) apoptosis induction of forodesine was studied

by annexin V staining as the indicator, and (b) antiproliferative effect of forodesine was studied by ^{3}H-thymidine incorporation into cells as the indicator. In the presence of dGuo, forodesine's apoptosis induction and antiproliferative effect were observed in CEM cell lines. These effects were not observed in MJ or Hut-78 cell lines.

- The effect of forodesine on cellular 2′-deoxynucleotide triphosphate (dNTP) concentration was studied in CEM cell lines by polymerase assay. In the presence of dGuo, the cellular concentration of dGTP increased by 154.4 ± 20.1 (mean ± standard error) fold (n = 3) that in the absence of dGuo. Forodesine's antiproliferative effect and effect on cellular dGTP decreased in the presence of dCyt.

No antiproliferative effect of forodesine was observed in human cell lines other than T-cell derived malignancies (MCF7 breast cancer cell line, DLD-1 colon cancer cell line, A-498 renal cell carcinoma cell line, HL-60 promyelocytic leukemia cell line, H33HJ-JA1 lymphoma cell line, SK-MEL-5 malignant melanoma cell line, PC-3 prostate cancer cell line, A-431 epidermoid carcinoma cell line, and MGL8 B lymphoblastoid cell line) regardless of the presence or absence of dGuo.

3.1.4 Effects on graft-versus-host (GVH) response and delayed-type hypersensitivity response (CTD 4.2.1.1.9, 4.2.1.1.10, and 4.2.1.1.11)

- Following a single peritoneal dose of anti-asialo GM1 antibody and pretreatment irradiation, human PBL was intraperitoneally administered to induce graft-versus-host disease (GVHD) in severe combined immunodeficient (SCID) mice (n = 5/group). Five days before PBL administration, forodesine 10 mg/kg bis in die (BID) was orally administered to these SCID mice to study survival. Statistically significant prolonged survival was observed in the forodesine group as compared with the control group (0.5% carboxymethyl cellulose) ($P < 0.001$, t-test).
- Delayed-type hypersensitivity response was induced in Balb/c mice by applying 0.5% 2,4-dinitorofluorobenzene (DNFB) 25 μL to the abdominal region on Days 0 and 1, and 0.3% DNFB 20 μL on both sides of the right auricle on Day 5. Forodesine 30 mg/kg quaque die (QD) was orally administered on Days 0 to 5, and the suppressive effect of forodesine on delayed-type hypersensitivity response was studied using auricular swelling as the indicator. No suppressive effect of forodesine on delayed-type hypersensitivity response was observed.
- GVH response was induced by intraperitoneally administering C57BL/6 mouse splenocytes in B6C3F1 mice [5)] (n = 4 to 7/group), and forodesine was administered at 30 mg/kg QD intraperitoneally, or 30 mg/kg QD or 50 mg/kg ter in die (TID) orally to study the suppressive effect of forodesine on GVH response using the spleen-to-body weight ratio on Day 10 as the indicator. No suppressive effect of forodesine on GVH response was observed either by intraperitoneal or oral dose.

5) Hybrid mice, a cross between C57BL/6 and C3H/He mice

3.2 Safety pharmacology

3.2.1 Effects on the central nervous system (CTD 4.2.1.3.1)

Rats (n = 6/group) received a single intravenous dose of forodesine 10, 30, or 100 mg/kg, and the effects of forodesine on clinical signs and behavior were studied using the Irwin's test. Mild and transient skin flush occurred. The applicant explained that because the mild and transient skin flush is unlikely to be of safety concern in the clinical use of forodesine.

3.2.2 Effects on the cardiovascular system

3.2.2.1 Effects on human *ether-a-go-go* related gene (hERG) potassium current (CTD 4.2.1.3.2)

The effects of forodesine on hERG potassium current were studied using hERG transfected human embryonic kidney cell line 293 (HEK293). The percentage inhibition of hERG potassium current (mean ± standard error) at 3000 μmol/L, the maximum concentration of forodesine studied, was 6.3 ± 0.1%. The IC_{50} was not able to be calculated.

3.2.2.2. Effects on heart rate, blood pressure, and electrocardiogram (ECG) (CTD 4.2.1.3.3 [reference data], 4.2.1.3.4)

Rats (n = 8) received a single intravenous dose of forodesine 50 and 150 mg/kg in sequential order, and its effect on heart rate and blood pressure was studied. A slight increase in heart rate was observed following the administration of forodesine 50 mg/kg, while no effects were observed at 150 mg/kg. No effects of forodesine on blood pressure were observed.

Cynomolgus monkeys (n = 4) received a single intravenous dose of forodesine 10, 30, or 90 mg/kg using a Latin square design, and its effect on heart rate, blood pressure, and ECG (i.e., PR, QRS, RR, QT, and QTc intervals, and R amplitude) were studied. No effects of forodesine were observed.

3.2.2.3 Effects on the respiratory system (CTD 4.2.1.3.5)

Rats (n = 6/group) received a single intravenous dose of forodesine 10, 30, or 100 mg/kg, and effects on respiratory rate, tidal volume, and minute volume were studied. No effects of forodesine were observed.

3.R Outline of the review conducted by PMDA

Based on the data submitted and the following discussions, PMDA concluded that forodesine may be effective against PTCL.

3.R.1 Mechanism of action of forodesine and its efficacy against PTCL

The applicant's explanation about the mechanism of action of forodesine and its efficacy against PTCL: PNP catalyzes the phosphorolysis of purine nucleosides such as dGuo and deoxyinosine to produce the bases and deoxyribose-1-phosphate. Forodesine is a low-molecular weight compound that inhibits PNP. PNP inhibition increases the intracellular accumulation of dGuo. Accumulated dGuo is then converted to dGTP by dCK, etc. Intracellular dGTP accumulation causes dNTP pool imbalances, induces apoptosis (*Molecules*. 2009;14:1183-226), and exhibits antiproliferative effects against tumors.

Data from non-clinical studies to examine the antiproliferative effects of forodesine on human PTCL cell lines are not available. Forodesine did not exhibit antiproliferative effect against MJ or Hut-78 cell lines derived from CTCL, a form of T-cell derived malignancy [see Section "3.1.3 Antiproliferative effects against lymphocytes and malignancies"]. However, the following observations from literature indicate that forodesine may exhibit efficacy against PTCL, a form of T-cell malignancy, through its PNP inhibitory effect, which increases dGTP accumulation in T-cell derived malignant tumor cells, thereby inducing apoptosis.

- Patients with PNP deficiency undergo T-cell depletion. Therefore, PNP is necessary for T-cell proliferation (*Immunodefic Rev.* 1991;3:45-81).
- In T-cells, dCK converts dGuo to dGTP relatively more actively than in other cells. In contrast, the conversion activity of nucleotidase from dGTP to dGuo is low (e.g., *Science.* 1981;214:1137-9).

PMDA's view:
In the main, PMDA accepted the applicant's explanation. However, the antiproliferative effect of forodesine was not observed on CTCL-derived cell lines, while CTCL is another T-cell derived malignancy like PTCL. This precludes an explanation of the efficacy of forodesine in the treatment of PTCL on the grounds that PTCL is a form of T-cell derived malignancy. Influential factors of the efficacy of forodesine against PTCL may be important in predicting the efficacy in its clinical use or identifying suitable patients. Therefore, data collection should be continued, and new findings should be communicated to healthcare professionals in an appropriate manner.

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

Pharmacokinetics (PK) of forodesine was studied in mice, rats, and monkeys. Plasma protein binding, drug-metabolizing enzymes, transporters, and other studies of forodesine were performed using human or animal biomaterials.

4.1 Absorption

4.1.1 Single-dose studies

A single dose of forodesine 10 mg/kg was administered intravenously or orally to non-fasted female mice, and plasma forodesine concentration was studied (Table 5). The bioavailability (BA) of oral forodesine 10 mg/kg was 63%.

A single intravenous dose of forodesine 1 mg/kg, or a single oral dose of forodesine 1, 5, or 10, or 20 mg/kg was administered to non-fasted male rats, and plasma forodesine concentration was studied (Table 5). The C_{max} and AUC_{all} of forodesine increased generally in a dose proportional manner over the dose range studied. The BA of oral forodesine 1 mg/kg was 11.1%.

A single intravenous dose of forodesine 1, 5, or 10 mg/kg, or a single oral dose of forodesine 5, 10, or 20 mg/kg was administered to non-fasted male monkeys, and plasma forodesine concentration was

studied (Table 5). The C_{max} and AUC_{all} of oral forodesine increased in a less than dose-proportional manner over the dose range studied. Based on the low membrane permeability of forodesine [see Section "4.1.3 *In vitro* membrane permeability"], the applicant explained that the less than dose-proportional increase may be attributable to the decreased absorption of forodesine with increasing dose levels. The C_{max} and AUC_{all} of intravenous forodesine increased generally in a dose proportional manner over the dose range studied. The BA of oral forodesine was 13.0% at 5 mg/kg and 8.41% at 10 mg/kg.

Table 5. PK parameters of forodesine in animals (single intravenous or oral dose)

Animal species	Route of administration	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	t_{max} (h)	AUC_{all} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h)
Mouse[*1]	Intravenous	10	F	4	5.96	0.083	4.74	0.77	–
	Oral	10	F	4	0.879	0.625	2.97	2.15	–
Rat	Intravenous	1	M	5	2.03 ± 0.45	0.08 ± 0	2.62 ± 1.21	1.08 ± 0.25	101 ± 40.0
	Oral	1	M	6	0.04 ± 0.04	6.33 ± 4.41	0.29 ± 0.17	26.76[*2]	–
		5	M	7	0.24 ± 0.19	3.00 ± 3.42	1.40 ± 0.63	7.04 ± 7.95	–
		10	M	7	0.20 ± 0.04	2.00 ± 2.65	1.46 ± 0.71	6.78 ± 5.76	–
		20	M	5	0.59 ± 0.41	5.20 ± 3.83	6.54 ± 4.79	8.45 ± 7.17	–
Monkey	Intravenous	1	M	3	1.20 ± 0.18	0.08 ± 0	3.12 ± 0.53	1.93 ± 0.68	1262 ± 178.2
		5	M	3	3.75 ± 0.63	0.22 ± 0.24	7.71 ± 4.01	2.48 ± 0.31	2221 ± 182.5
		10	M	3	12.0 ± 3.52	0.08 ± 0	19.45 ± 4.70	2.83 ± 1.08	2135 ± 258.8
	Oral	5	M	3	0.04 ± 0.02	11.3 ± 11.4	0.80 ± 0.46	–	–
		10	M	3	0.10 ± 0.04	8.67 ± 5.77	1.69 ± 0.73	–	–
		20	M	3	0.10 ± 0.04	3.33 ± 1.15	1.28 ± 0.35	–	–

Mean ± standard deviation; M, male; F, female; [*1] PK parameters were calculated based on the mean of plasma forodesine concentrations at all measuring time points; [*2] n = 1; –, not calculated.

A single intravenous dose of ^{14}C labeled forodesine hydrochloride[6)] 10 mg/kg or a single oral dose of ^{14}C labeled forodesine hydrochloride[6)] 100 mg/kg was administered to male and female non-fasted monkeys, and the levels of radioactivity in blood and plasma were studied. No clear difference was observed between the sexes in the blood and plasma radioactivity levels after intravenous or oral administration. Following intravenous administration, the Vd of plasma radioactivity exceeded 45 L/kg,[7)] which was higher than the body fluid of the monkey (approximately 0.7 L/kg) (*Pharm Res.* 1993;10:1093-5). The applicant therefore noted that the results are suggestive of the distribution of forodesine in many tissues.

4.1.2 Repeated-dose studies

Forodesine was administered at 13, 39, or 117 mg/kg QD orally to non-fasted male and female monkeys for 26 weeks to study the plasma concentration of forodesine (Table 6).

The C_{max} and AUC_{last} of forodesine increased in a less than dose-proportional manner over the dose range studied. The applicant explained that the less than dose-proportional increase may be attributable to the decreased absorption of forodesine with increased dose level because of the low membrane permeability [see Section "4.1.3 *In vitro* membrane permeability"]. No clear difference was observed between the sexes in the C_{max} and AUC_{last} of forodesine. Further, no clear effect of repeated doses on

6) Calculated as free base
7) Calculated based on the specific gravity of body fluid being taken as 1

C_{max} or AUC_{last} was observed.

Table 6. PK parameters of forodesine (male and female monkeys, 26-week repeated oral administration)

Measured date (Day)	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	t_{max} (h)	AUC_{last} (μg·h/mL)
0*	13	M	4	0.121 ± 0.0418	2.5 ± 1.0	1.430 ± 0.203
		F	4	0.179 ± 0.0384	2.5 ± 1.0	1.743 ± 0.352
	39	M	4	0.515 ± 0.135	2.5 ± 1.0	3.972 ± 0.846
		F	4	0.577 ± 0.221	1.5 ± 1.0	3.952 ± 1.126
	117	M	6	0.917 ± 0.205	2.0 ± 1.1	6.171 ± 0.990
		F	6	1.070 ± 0.217	1.3 ± 0.8	6.255 ± 0.595
87	13	M	4	0.144 ± 0.016	4.5 ± 1.7	2.105 ± 0.099
		F	4	0.117 ± 0.010	6.0 ± 0	1.759 ± 0.319
	39	M	4	0.327 ± 0.119	2.0 ± 1.2	3.782 ± 1.244
		F	4	0.323 ± 0.039	3.8 ± 1.5	3.887 ± 0.674
	117	M	6	0.629 ± 0.064	1.7 ± 1.0	6.507 ± 0.723
		F	6	0.756 ± 0.137	2.0 ± 1.1	8.278 ± 1.344
175	13	M	4	0.171 ± 0.038	1.3 ± 1.3	2.529 ± 0.457
		F	4	0.167 ± 0.026	4.0 ± 2.4	2.522 ± 0.438
	39	M	4	0.289 ± 0.127	3.3 ± 2.1	3.779 ± 0.773
		F	4	0.292 ± 0.0155	3.3 ± 2.1	4.048 ± 0.840
	117	M	6	0.565 ± 0.132	1.7 ± 1.0	5.457 ± 1.221
		F	6	0.623 ± 0.151	3.2 ± 1.6	6.964 ± 1.317

Mean ± standard deviation; M, male; F, female; * the first treatment day

4.1.3 *In vitro* membrane permeability

The membrane permeability of forodesine was studied using human colon cancer cell line Caco-2. The apparent permeability in apical to basolateral direction ($P_{app\ A\rightarrow B}$) of forodesine (5 μmol/L) was 0.32×10^{-6} cm/sec, whereas that of ^{14}C-labeled mannitol (10 μmol/L), the negative control, was 1.31×10^{-6} cm/sec. The applicant explained that the membrane permeability of forodesine is considered to be low based on the results.

4.2 Distribution

4.2.1 Tissue distribution

A single intravenous dose of 10 mg/kg[6)] of ^{14}C-labeled forodesine hydrochloride was administered to male and female albino rats, and a single intravenous dose of 10 mg/kg,[6)] or single oral dose of 100 mg/kg[6)] of ^{14}C-labeled forodesine hydrochloride was administered to male pigmented rats to study the tissue distribution of radioactivity. Tissue radioactivity levels were measured 2 to 72 hours post-dose in albino rats, and 8 to 504 hours post-dose in pigmented rats.

In albino rats, the highest radioactivity levels were observed at 2 hours post-dose in the bladder (48.3 and 78.3 μg Eq./g in female and male rats, respectively). Overall, radioactivity levels were higher in the tissues than in plasma. The tissue-to-plasma radioactivity ratio increased over time. The applicant explained that the results suggest that plasma to tissue transfer of forodesine or elimination of forodesine from plasma is faster than the elimination of forodesine from tissues. In pigmented rats, radioactivity

was detected in the eye, skin, and fat at 504 hours following the intravenous or oral dose.

4.2.2 Plasma protein binding and transfer to blood cells

Forodesine (0.1-100 μmol/L) was incubated in rat, dog, monkey, or human plasma at 37°C for 15 minutes, and binding of forodesine with plasma proteins was studied using an ultrafiltration method. Binding rate of forodesine to plasma protein was 0% to 28% in rats, 1.1% to 38% in dogs, 0% to 61% in monkeys, and 0.2% to 32% in humans.

A single intravenous dose of 10 mg/kg[6)] of ^{14}C-labeled forodesine hydrochloride or a single oral dose of 100 mg/kg[6)] of ^{14}C-labeled forodesine hydrochloride was administered to male and female monkeys, and transfer of forodesine to blood cells was studied. The blood-to-plasma radioactivity ratio remained at approximately 1 up to 4 hours post-oral dose and 8 hours post-intravenous dose, and began increasing over time to 4.2 at 96 hours post-oral dose and 9.2 at 72 hours post-intravenous dose, reaching steady state. The applicant explained that the results demonstrated more rapid radioactivity elimination in plasma than in blood.

4.2.3 Transfer across the placenta to fetus

The transfer of forodesine across the placenta was not evaluated. However, because of delayed ossification observed in embryos and fetuses in a rabbit embryo-fetal development study [see Section "5.5.2 Rabbit embryo-fetal development toxicity study"], the applicant explained that the possibility of forodesine transfer across the placenta to the fetus could be ruled out.

4.3 Metabolism

The applicant explained that the following results suggest hepatic metabolism does not play a major role in the elimination of forodesine:

- After incubating forodesine (5 μmol/L) in rat, monkey, and human liver microsomes at 37°C for 60 minutes, the residual rate of forodesine was 102%, 96%, and 98%, respectively.
- In studies in male and female rats and male and female monkeys, a single intravenous dose of ^{14}C-labeled forodesine hydrochloride 10 mg/kg[6)] or a single oral dose of ^{14}C-labeled forodesine hydrochloride 100 mg/kg[6)] was administered. The results showed that only unchanged forodesine was detected in plasma, and no forodesine metabolites were detected.

4.4 Excretion

4.4.1 Urinary and fecal excretion

A single intravenous dose of ^{14}C-labeled forodesine hydrochloride 10 mg/kg[6)] or a single oral dose of ^{14}C-labeled forodesine hydrochloride 100 mg/kg[6)] was administered to male and female rats and male and female monkeys to study urinary and fecal excretion rates of forodesine (percentage to the administered radioactivity). Based on the results shown below, the applicant explains that oral forodesine is excreted primarily in feces and intravenous forodesine primarily in urine.

- In the study in rats of both sexes, urinary and fecal excretion rates up to 72 hours post-oral dose

were, respectively, 7.45% and 93.6% in male rats and 6.61% and 86.4% in female rats. In contrast, urinary and fecal excretion rates up to 72 hours post-intravenous dose were, respectively, 84.3% and 2.61% in male rats and 87.6% and 2.49% in female rats.

- In the study in monkeys of both sexes, urinary and fecal excretion rates up to 168 hours post-oral dose were, respectively, 1.37% and 82.5% in male monkeys and 2.66% and 78.8% in female monkeys. Urinary and fecal excretion rates up to 168 hours post-intravenous dose were, respectively, 7.25% and 4.47% in male monkeys and 23.9% and 4.34% in female monkeys. The total recovery rates including the radioactivity detected in cage washings were 77.8% and 61.5% in female and male animals, respectively.

4.4.2 Excretion in breast milk

The excretion of forodesine in breast milk has not been investigated. The applicant, however, explained that forodesine, being weakly basic and having low protein binding, may be excreted in breast milk [see Section "4.2.2 Plasma protein binding and transfer to blood cells"].

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

In the presence of forodesine (10 μmol/L), substrates for cytochrome P450 (CYP) isoforms (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A)[8)] were incubated with human liver microsomes to study the inhibitory effect of forodesine against CYP isoforms. Forodesine did not show clear inhibitory effect against the metabolism of any of the CYP substrates studied.

4.5.2 Enzyme induction

Human hepatocytes were treated with forodesine (1, 10, or 100 μmol/L) for 3 days, and the enzyme activity of CYP isoforms (CYP1A2 and CYP3A) was studied. Forodesine did not clearly induce activity of either of the CYP isoforms.

4.5.3 Transporters

The P-glycoprotein (P-gp)-mediated transport of forodesine (5 μmol/L) was studied using Caco-2 cell lines. The ratio of the secretory permeability to the absorptive permeability (efflux ratio) of forodesine in the presence and absence of the P-gp inhibitor (verapamil 100 μmol/L) was 1.71 and 1.41, respectively. The applicant explained that the results suggest that forodesine is not a substrate for P-gp.

The inhibitory effect of forodesine (0.05, 0.5, and 5 μmol/L) on P-gp-mediated transport of ^{3}H-labeled digoxin (1 μmol/L) was studied using the Caco-2 cell line. Forodesine did not show clear inhibitory effect against P-gp-mediated transport.

4.R Outline of the review conducted by PMDA

8) 7-Ethoxyresorufin, coumarin, tolbutamide, S-mephenytoin, bufuralol, chlorzoxazone, and midazolam were used as the substrates for CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A, respectively.

Based on the submitted data and the following review, PMDA concluded that the applicant's discussions on absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of forodesine are acceptable.

4.R.1 Tissue distribution

PMDA asked the applicant to explain the possibility that the distribution of forodesine in melanin-containing tissues may become a safety concern in clinical use, given that the results of a study suggested that the elimination of forodesine from tissues could be slower in pigmented rats than in albino rats [see Section "4.2.1 Tissue distribution"].

The applicant's explanation:

Based on the following observations, the distribution of forodesine in melanin-containing tissues is unlikely to raise a safety concern in the clinical use of forodesine:

- In the 6-month repeated oral dose toxicity study in monkeys, forodesine caused no toxicity in the eye and skin [see Section "5.2.4 Six-month repeated oral-dose toxicity study in monkeys"].
- In Study J02, a causal relationship to forodesine could not be ruled out for Grade ≥3 eye and skin or subcutaneous tissue disorders, namely, erythema multiforme, pustular psoriasis, and rash maculo-papular (1 subject each). None of these events are attributable to the distribution of forodesine in melanin-containing tissues.

PMDA accepted the applicant's explanation.

4.R.2 Transporter-mediated pharmacokinetic interactions

No data on pharmacokinetic interactions mediated by transporters other than P-gp were submitted with the application. Therefore, PMDA asked the applicant to explain the reasons for not conducting such studies.

The applicant's explanation:

Based on the following observations, pharmacokinetic interactions mediated by non- P-gp transporters are unlikely to occur. Relevant studies were thus omitted.

- Hepatic metabolism was not suggested to be a major route of the elimination of forodesine [see Section "4.3 Metabolism"]. Therefore, hepatic transporters are unlikely to play a significant role in the elimination of forodesine.
- Study J02 revealed no safety concern due to the interaction.

PMDA's view:

The pharmacokinetic interactions of forodesine mediated by non-P-gp transporters are unclear at present because of no studies conducted. Data on pharmacokinetic interactions of forodesine mediated by transporters are important for the proper use of forodesine, and relevant data should be collected. Useful findings should be communicated to healthcare professionals in an appropriate manner.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

While no single-dose toxicity studies of forodesine were conducted, the acute toxicity of forodesine was evaluated based on the results of the high-dose group following the first dose of the repeated-dose toxicity study [see Section "5.2 Repeated-dose toxicity"].

In repeated oral dose toxicity studies, oral forodesine 50, 270, and 720 mg/kg were administered to mice (21 days), rats (6 months), and cynomolgus monkeys (13 weeks). No deaths or changes in clinical signs associated with forodesine were observed. Accordingly, the approximate lethal oral dose was determined to be >50, 270, and 720 mg/kg for mice, rats, and cynomolgus monkeys, respectively.

In repeated intravenous dose toxicity studies, intravenous forodesine 150 and 90 mg/kg were administered to rats and cynomolgus monkeys, respectively, for 14 days. No deaths or changes in clinical signs associated with forodesine were observed. Accordingly, the approximate lethal intravenous dose was determined to be >150 and 90 mg/kg for rats and cynomolgus monkeys, respectively.

5.2 Repeated-dose toxicity

5.2.1 Twenty-one-day repeated oral-dose toxicity study in mice

Oral forodesine 0 (vehicle, 0.5% carboxymethyl cellulose solution), 5, or 50 mg/kg QD were administered to mice (CD-1; 10 males each in the control and 50 mg/kg groups, 5 males in the 5 mg/kg group) for 21 days. The 5 animals each in the control and 50 mg/kg groups had a 14-day recovery period after the completion of treatment.

No deaths associated with forodesine occurred. In the 50 mg/kg group, low red blood cell count, low hemoglobin levels, low hematocrit, and increased heart weight were observed. However, there were no related histopathological findings. All changes resolved after the 14-day recovery period.

Accordingly, the no-observed-adverse-effect level (NOAEL) for the study was determined to be 50 mg/kg/day.

5.2.2 Six-month repeated oral-dose toxicity study in rats

Oral forodesine 0 (vehicle, deionized water), 30, 90, or 270 mg/kg QD were administered to rats (SD; 30/sex each in the control and 270 mg/kg groups; 20/sex each in the 30 and 90 mg/kg groups) for 6 months. Ten each of male and female rats in the control and 270 mg/kg groups had a 28-day recovery period after the completion of treatment.

No forodesine-related deaths occurred. The following changes were noted at ≥30 mg/kg: high urine specific gravity; decreased urine output; desquamation of the tail; scab formation, expansion, and

reddening in the anogenital and urogenital regions; expansion and reddening in the auricular region; increased spleen and adrenal weights; lymphocyte necrosis in the thymus; increased bone marrow cellularity; lymphocyte hyperplasia and brown pigmentation in the spleen; monocyte infiltration and inflammation in the kidney; inflammation and ulcer in the tail; and hyperplasia and brown pigmentation in the adrenal cortex. Changes observed at ≥90 mg/kg were inflammation in the auricular region, increased liver weight; congested liver, and monocyte infiltration and inflammation in the liver and lung. Changes observed at 270 mg/kg were low eosinophil count, increased kidney and heart weights, atrophy of the thymus, monocyte infiltration and inflammation in the heart and pancreas, single cell necrosis in the pancreatic exocrine cells, thyroid C-cell hyperplasia, and cardiomyopathy. After the 28-day recovery period, increased bone marrow cellularity, increased spleen weight, inflammation in the lung, hyperplasia and brown pigmentation in the adrenal cortex, and congested liver were still observed at 270 mg/kg. Thyroid C-cell hyperplasia observed at 270 mg/kg was probably a spontaneous change in rats due to aging. Single cell necrosis in the exocrine pancreas and cardiomyopathy also observed at 270 mg/kg were not detected in the 13-week repeated oral dose toxicity study in monkeys, and the clinical studies revealed no findings suggestive of these events. Therefore, the applicant explained that thyroid C-cell hyperplasia and single cell necrosis in the exocrine pancreas and cardiomyopathy are unlikely to occur in the clinical use of forodesine.

Accordingly, the NOAEL for the study was determined to be <30 mg/kg/day.

In this study, C_{max} of forodesine 30 mg/kg (0.44 to 0.61 μg/mL) was 0.63 to 0.87-fold that of the clinical exposure to forodesine,[9)] $AUC_{0\text{-}24h}$ (3.29 to 3.50 μg·h/mL) was 0.25 to 0.27-fold that of the clinical exposure to forodesine.[9)]

5.2.3 Thirteen-week repeated oral-dose toxicity study in monkeys

Oral forodesine 0 (vehicle, purified water), 120, 300, or 720 mg/kg BID were administered to cynomolgus monkeys (8/sex each in the control and 720 mg/kg groups; 4/sex each in the 120 and 300 mg/kg groups) for 13 weeks. Four each of male and female monkeys in the control and 720 mg/kg groups underwent a 4-week recovery period after the completion of treatment period.

No deaths associated with forodesine treatment were observed. At ≥120 mg/kg, low levels of white blood cell count and lymphocyte count, and decreased size, darkening, and atrophy of the thymus were observed. Pale color feces was observed at ≥300 mg/kg. At ≥720 mg/kg, increased body weight gain, and lymphoid tissue hyperplasia in the mandibular lymph nodes, mesenteric lymph nodes, and spleen were observed. After the 4-week recovery period, all changes resolved. The lymphoid tissue hyperplasia in the mandibular lymph nodes, mesenteric lymph nodes, and spleen was determined to have been associated with the pharmacological effect of forodesine. However, the applicant explained the that the changes are unlikely to pose a safety concern in the clinical use of forodesine because (a) the changes

9) In the Japanese Phase I/II study (Study J02), following oral dose of forodesine 300 mg BID to patients with PTCL, the C_{max} was 0.699 μg/mL. The $AUC_{0\text{-}24h}$ estimated from AUC_{tau} (AUC during a 12-hour dosing interval at steady state), 6.52 μg·h/mL, was 13.04 μg·h/mL.

were infrequent and mild, (b) and resolved in the monkeys given the recovery period; and (c) the adverse event related to these changes (lymphadenitis) observed in Study J02 was mild.

Based on the above, the NOAEL for the study was determined to be 1440 mg/kg/day.

At the NOAEL of this study, C_{max} (3.48 to 5.04 μg/mL) was 4.98 to 7.21-fold that of the clinical exposure level to forodesine,[9)] and $AUC_{0\text{-}24h}$ (51.5 to 66.2 μg·h/mL) was 3.95 to 5.08-fold that of the clinical exposure level to forodesine.[9)]

5.2.4 Six-month repeated oral-dose toxicity study in monkeys

Oral forodesine 0 (vehicle, deionized water), 13, 39, or 117 mg/kg QD were administered to cynomolgus monkeys (6/sex each in the control and 117 mg/kg groups; and 4/sex each in the 13 and 39 mg/kg groups) for 6 months. Two each of male and female monkeys in the control and 117 mg/kg groups underwent a 28-day recovery period after the treatment period.

There were no deaths associated with forodesine treatment. At ≥13 mg/kg, low white blood cell count, decreased thymus weight and size, and lymphocyte depletion in the thymus, and increased apoptosis in the thymus were observed. At ≥39 mg/kg, low lymphocyte count was observed. These changes were determined to be the pharmacological effects of forodesine. After the 28-day recovery period, all changes either resolved or were resolving.

Based on the above, the NOAEL for the study was determined to be 117 mg/kg/day.

At the NOAEL of this study, C_{max} (0.57 to 0.62 μg/mL) was 0.82 to 0.89-fold that of the clinical exposure level to forodesine,[9)] and $AUC_{0\text{-}24h}$ (5.46 to 6.96 μg·h/mL) was 0.42 to 0.53-fold that of the clinical exposure level to forodesine.[9)]

5.2.5 Twenty-eight-day repeated intravenous dose toxicity study in rats [reference data]

Intravenous forodesine 0 (vehicle, Ringer's lactate solution), 5, 15, or 50 mg/kg BID were administered to rats (Wistar; 7/sex each in the control and 50 mg/kg groups; 5/sex each in the 5 and 15 mg/kg groups) for 28 days. Two each of male and female rats in the control and 50 mg/kg groups underwent a 21-day recovery period after the treatment period. A histopathological examination was performed only in the control and 50 mg/kg groups.

There were no deaths associated with forodesine. Observed changes in the animals receiving ≥5 mg/kg were low total protein and globulin levels, while those receiving ≥15 mg/kg had low cholesterol. Animals receiving 50 mg/kg experienced low hemoglobin and hematocrit levels, high aspartate aminotransferase (AST) level, increased kidney, liver, lung, and thyroid/parathyroid weights, interstitial cell infiltration in the pancreas and kidney, and projections in Kupffer cells in the liver.

5.2.6 Twenty-eight-day repeated intravenous dose toxicity study in monkeys

Intravenous forodesine 0 (vehicle, Ringer's lactate solution), 10, 30, or 90 mg/kg QD were administered to cynomolgus monkeys (5/sex in the 90 mg/kg group; 3/sex each in the control, 10 and 30 mg/kg groups) for 28 days. Two each of male and female monkeys in the 90 mg/kg groups underwent a 2-week recovery period after the treatment period.

There were no deaths associated with forodesine treatment. The following changes were noted: at ≥10 mg/kg, decreased thymus weight, and lymphocyte depletion; at 90 mg/kg, low neutrophil counts, high blood creatinine level, and aggravated lymphocyte depletion in the thymus. After the 2-week recovery period, all changes either resolved or were resolving.

Because lymphocyte depletion in the thymus aggravated in the 90 mg/kg group, the NOAEL for the study was determined to be 30 mg/kg/day.

5.3 Genotoxicity [Bacterial reverse mutation assay and chromosomal aberration assay in Chinese hamster ovary cells were reference data]

In vitro genotoxicity studies consisted of a bacterial reverse mutation assay and a chromosomal aberration assay in human peripheral blood lymphocytes and Chinese hamster ovary (CHO) cells. *In vivo* genotoxicity studies consisted of a micronucleus assay in rat bone marrow. In the chromosomal aberration assay in human peripheral blood lymphocytes, structural chromosome aberration and aneuploidy were observed after 24 hour-treatment in the absence of S9 mix. However, the change was considered related to apoptosis induction of forodesine and of no genotoxicity. The reverse mutation assay, chromosomal aberration assay in CHO cells, and in the micronucleus assay were negative. Based on the results, forodesine is non-genotoxic.

5.4 Carcinogenicity

No carcinogenicity study has been performed because forodesine is intended for the treatment of patients with advanced-stage cancer.

5.5 Reproductive and developmental toxicity

Embryo-fetal development studies in rats and rabbits were conducted to study reproductive and developmental toxicity.

The applicant's explanation about the effects of forodesine on fertility:
Forodesine is unlikely to have an impact on fertility because of no forodesine-associated histopathological changes observed in the reproductive organs of mice, rats, and monkeys in repeated-dose toxicity studies.

5.5.1 Rat embryo-fetal development toxicity study

Intravenous forodesine 0 (vehicle, normal saline), 15, 45, or 120 mg/kg QD were administered to

pregnant rats (SD; 25/group) on Gestation Days 7 to 17.

In dams, suppressed body weight gain and decreased food intake were noted at ≥45 mg/kg. In embryos and fetuses, delayed ossification was observed in caudal vertebra and metatarsal bones of the hindlimb at 120 mg/kg. No malformation or variation was observed in the appearance, internal organs, and skeleton of embryos or fetuses.

Based on the above, the NOAEL of this study was determined to be 15 mg/kg/day for general toxicity in dams, and 45 mg/kg/day for embryo-fetal development.

At the NOAELs of this study, the C_{max} for dams and embryo-fetal development (8.20 and 24.60 μg/mL) were 11.7 and 35.2-fold that of the clinical exposure to forodesine,[9)] respectively; and $AUC_{0\text{-}24h}$ for dams and embryo-fetal development (19.66 and 58.98 μg·h/mL) were 1.51 and 4.52-fold that of the clinical exposure to forodesine,[9)] respectively.

5.5.2 Rabbit embryo-fetal development toxicity study

Intravenous forodesine 0 (vehicle, normal saline), 15, 45, or 120 mg/kg QD were administered to pregnant rabbits (NZW; 20/group) on Gestation Days 7 to 19.

In dams, suppressed body weight gain and decreased food intake were noted at 120 mg/kg. The following findings were noted in embryos and fetuses: delayed ossification in metatarsal bones of the forelimb at ≥15 mg/kg; and delayed ossification in caudal vertebra and phalanx of the forelimb at ≥45 mg/kg. Because delayed ossification in metatarsal bones of the forelimb was the only finding in the 15 mg/kg group, it was not identified as toxicity. No malformation or variation was observed in the appearance, internal organs, and skeleton of embryos/fetuses.

Based on the above, the NOAEL for this study was determined to be 45 mg/kg/day for general toxicity in dams, and 15 mg/kg/day for embryo-fetal development.

At the NOAELs of this study, C_{max} for dams and embryo-fetal development (14.3 and 4.42 μg/mL) were 20.46 and 6.32-fold that of the clinical exposure to forodesine,[9)] respectively; and $AUC_{0\text{-}24h}$ for dams and embryo-fetal development (45.7 and 14.5 μg·h/mL) were 3.50 and 1.11-fold that of the clinical exposure to forodesine,[9)] respectively.

5.6 Other toxicity studies

5.6.1 Combined administration with bendamustine and rituximab

Oral forodesine 0 (vehicle, purified water) or 120 mg/kg QD were administered to cynomolgus monkeys (5 females/group)[10)] in combination with rituximab or bendamustine hydrochloride (referred to as

[10)] The treatment groups:(a) forodesine 0 mg/kg and rituximab, (b) forodesine 120 mg/kg and rituximab, (c) forodesine 0 mg/kg and rituximab plus bendamustine, and (d) forodesine 120 mg/kg and rituximab plus bendamustine

bendamustine) for 31 days. Rituximab 31.25 or 41.66 mg/kg was administered intravenously on Days 1 and 29. Bendamustine 5.83 mg/kg was administered intravenously on Days 1, 2, 29, and 30. Two monkeys underwent a 4-week recovery period after the treatment period.

The combination therapies with forodesine did not aggravate toxicity changes as compared with those in the rituximab monotherapy or in the combination therapy of rituximab and bendamustine.

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that in the non-clinical toxicity evaluation, no problems are associated with the clinical use of forodesine.

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

There were 2 oral formulations of forodesine, one for clinical studies (100 mg capsule) and the other as commercial formulation (100 mg capsule). The PK, etc. of forodesine were investigated using both formulations.

Table 6. Formulations used in clinical studies

Formulation	Study
Clinical study formulation*1	Foreign Phase I study (Studies BCX1777-Hio-05-107 and BCX1777-111), foreign Phase I/II study (Study 105), and foreign Phase II study (Study 204)
Commercial formulation*2	Japanese Phase I study (Study J01), Japanese Phase I/II study (Study J02), foreign Phase I study (Study BCX1777-111, Studies 112 and 116), foreign Phase I/II study (Study 105), and foreign Phase II study (Studies 203, 204, and 210)

*1 Formulation produced by direct mixing; *2 formulation produced by fluidized bed granulation

6.1.1 Assay

The concentrations of forodesine in human plasma and urine were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS), and the lower limits of quantitation were 2.5 ng/mL[11] and 10 ng/mL,[12] respectively.

6.1.2 Foreign clinical studies

6.1.2.1 Foreign Phase I study (CTD 5.3.1.2.1, Study BCX1777-111 [[redacted] to [redacted] 20[redacted]])

A 2-treatment, 2-period, crossover study was conducted in 36 healthy adults (33 subjects were included in the PK analysis set) to assess the bioequivalence between the clinical study formulation and the commercial formulation. A single oral dose of forodesine 200 mg was administered in the fasted state, and a 34-day washout period was given between the 2 periods.

The geometric mean ratios of the clinical study formulation to the commercial formulation for C_{max}, $AUC_{0\text{-}72h}$, and AUC_{last} of forodesine were 1.000 (90% confidence interval [CI], 0.897-1.116), 1.028

11) In Studies BCX1777-Hio-05-107 and 105, specimens were measured by quantification methods with a lower limit of quantitation of 5 ng/mL.

12) Some specimens in Study BCX1777-Hio-05-107 were measured by quantification methods with a lower limit of quantitation of 5000 ng/mL, and all specimens in Study J02 with a lower limit of quantitation of 2.5 ng/mL.

(90% CI, 0.969-1.090), and 1.037 (90% CI, 0.983-1.095), respectively. The 90% confidence intervals for C_{max}, AUC_{0-72h}, and AUC_{last} of forodesine fell between 0.80 and 1.25, the bioequivalence criteria.

The applicant explained that the above results demonstrated the bioequivalence between the clinical study formulation and the commercial formulation.

6.1.2.2 Foreign Phase I study (CTD 5.3.1.1.1, Study BCX1777-Hio-05-107 [to 20])

A 6-treatment, 3-period, crossover study was conducted in 18 healthy adults (18 subjects were included in the PK analysis set) to assess food effect and absolute BA. Using the clinical study formulation, a single oral dose of forodesine 300 mg was administered in the fasted state (fasting from 10 hours pre-dose through 4 hours post-dose) or within 30 minutes after the completion of a high-fat meal (the total calories of the meal were approximately 800-1000 kcal, consisting of approximately 50% fat), or a single intravenous dose of forodesine 40 mg/m^2 was administered in the fasted state, to evaluate plasma and urinary forodesine concentrations. A 20-day washout period was given between the treatment periods.

The geometric mean ratios of C_{max} and AUC_{inf} of the dose after a high-fat meal to that in the fasted state were 1.127 (90% CI, 0.984-1.291) and 1.184 (90% CI, 1.055-1.328), respectively. The median values of t_{max} were similar regardless of the meal condition. Exposure to forodesine was indicated to be increased by food intake. In the population pharmacokinetics (PPK) analysis, meal condition was not selected as a significant covariate for PK parameters of forodesine [see Section "6.2.3 PPK analysis"]. The applicant, therefore, explained that it is not necessary to specify meal condition in the "Dosage and administration" section. Further, the absolute BA of forodesine was 19.5% when administered orally in the fasted state, and 23.2% when administered orally after a high-fat meal. The urinary excretion rates (percentage to the dose) of forodesine up to 72 hours post-oral dose in the fasted state, oral dose after a high-fat meal, and intravenous dose were 12.5%, 14.1% and 91.0%, respectively.

6.1.3 The effect of gastric pH on the PK of forodesine

The solubility of forodesine was approximately 100, 10, and 5 mg/mL at pH 3, 5.8, and 7.6, respectively, indicating that the solubility decreased as pH increased. However, the dissolution behavior of forodesine from the formulation was similar over the range from pH 1.2 to 6.8. Therefore, the applicant explained that change in pH will not affect the dissolution of forodesine from the formulation, and that it is unlikely that an increase in gastric pH associated with low gastric acid condition, administration of proton pump inhibitors, etc. will affect the PK of forodesine.

6.2 Clinical pharmacology

The PK of forodesine in healthy adults and patients with cancer was assessed for forodesine monotherapy.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese Phase I study (CTD 5.3.3.2.1, Study J01 [January 2009 to July 2013])

An open-label, uncontrolled study was conducted in 13 patients with relapsed or refractory T/NK-cell tumors excluding T-acute lymphoblastic leukemia/T-acute lymphoblastic lymphoma (T-ALL/T-LBL) (13 subjects were included in the PK analysis set) to assess the PK, etc. of forodesine. Subjects received oral forodesine 100, 200, or 300 mg QD, and plasma forodesine concentrations were evaluated.

Table 7 shows the PK parameters of forodesine. A power model analysis was performed, and the applicant explained that the C_{max} and AUC of forodesine on Days 1 and 15 increased approximately in a dose proportional manner over the dose range studied.

Table 7. PK parameters of forodesine

Measured date (Day)	Dose (mg)	n	C_{max} (ng/mL)	t_{max} [*1] (h)	AUC[*2] (ng·h/mL)	$t_{1/2}$ (h)
1	100	5	139.2 ± 83.1	4.00 (3.98, 22.58)	1948.0 ± 883.6	13.01 ± 3.83[*3]
	200	3	335.3 ± 106.2	4.08 (1.95, 6.00)	4608.0 ± 1029.9	14.06 ± 10.32
	300	5	328.0 ± 64.0	4.00 (3.73, 5.77)	4595.6 ± 938.9	14.43 ± 6.84
15	100	4	216.5 ± 136.2	4.11 (2.05, 6.10)	2729.5 ± 1358.2	–
	200	3	499.0 ± 155.9	3.97 (3.88, 3.98)	6302.5 ± 1051.7	–
	300	5	421.6 ± 49.6	4.03 (3.93, 4.13)	5587.0 ± 920.3	–

Mean ± standard deviation; [*1] median (range); [*2] AUC_{last} on Day 1, AUC_{tau} on Day 15; [*3] n = 4; –, not calculated

6.2.1.2 Japanese Phase I/II study (CTD 5.3.5.2.1, Study J02 [ongoing since January 2013, data cut-off on August 3, 2015])

An open-label, uncontrolled study was conducted in 69 patients with relapsed or refractory PTCL[13)] (7 subjects were included in the PK analysis set) to assess the PK, etc. of forodesine. Subjects received oral forodesine 300 mg BID, and plasma forodesine concentrations were evaluated.

Table 8 shows the PK parameters of forodesine. The trough concentrations of forodesine in plasma were roughly consistent from Days 3 to 15.

13) Patients with ≥1 prior antineoplastic drug treatment who had aggravated symptoms after achieving PR or better by the most recent antineoplastic drug treatment.

Table 8. PK parameters of forodesine

Measured date (Day)	C_{max} (ng/mL)	t_{max} [*1] (h)	AUC [*2] (ng·h/mL)
1	450 ± 156	4.0 (3.9, 6.1)	3540 ± 1250
15	699 ± 157	4.0 (2.0, 6.0)	6520 ± 1660

Mean ± standard deviation; n = 7, [*1] median (range), [*2] AUC_{last} on Day 1 and AUC_{tau} on Day 15

6.2.2 Foreign clinical studies

6.2.2.1 Foreign Phase I study (CTD 5.3.4.1.1, Study 116 [to 20])

A 3-treatment, 3-period, crossover study was conducted in 54 healthy adults (49 subjects were included in the PK analysis set) to assess the PK, etc. of forodesine. Plasma forodesine concentrations were evaluated following (a) oral forodesine 200, 300, or 400 mg BID; (b) oral forodesine 400, 600, or 800 mg QD; and (c) intravenous forodesine 40 mg/m^2 QD. Subjects underwent a washout of ≥7 days between the treatment periods.

Table 9 shows the pharmacokinetic parameters of forodesine on Day 7 of each treatment period. Following BID oral doses, the C_{max} and $AUC_{0\text{-}24h}$ of forodesine increased from 200 mg/dose to 300 mg/dose with increasing dose levels. In contrast, the values remained approximately the same when the dose was increased from 300 mg to 400 mg. The C_{max} and $AUC_{0\text{-}24h}$ of forodesine following QD oral doses increased in a less than dose-proportional manner over the dose range studied. The applicant explained the less than dose-proportional increase of C_{max} and $AUC_{0\text{-}24h}$ might be attributable to the decreased absorption of forodesine with increasing dose levels, based on the low membrane permeability of forodesine [see Section "4.1.3 *In vitro* membrane permeability"].

Table 9. PK parameters of forodesine

Route of administration	Regimen	n	C_{max} (ng/mL)	t_{max} [*1] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	$AUC_{0\text{-}12h}$ (ng·h/mL)
Oral	200 mg BID	15	442 ± 123[*2]	3.50 (1.00, 4.52)[*2]	7840 ± 1861	3690 ± 1030[*2]
	300 mg BID	16	682 ± 269[*2]	3.50 (2.00, 4.50)[*2]	12,087 ± 4787	5850 ± 2290[*2]
	400 mg BID	17	733 ± 225[*2]	3.50 (3.00, 4.50)[*2]	12,500 ± 3369	6150 ± 1690[*2]
	400 mg QD	15	582 ± 272	4.50 (3.00, 6.05)	5955 ± 1114	4270 ± 891
	600 mg QD	16	716 ± 252	4.00 (2.88, 5.00)	8246 ± 3139	5730 ± 2100
	800 mg QD	18	802 ± 197	4.00 (3.00, 5.00)	8959 ± 1882	6410 ± 1460
Intravenous	40 mg/m^2 QD	47	1955 ± 352.3	0.50 (0.35, 0.53)	9499 ± 880.2	–

Mean ± standard deviation; [*1] median (range); [*2] based on the data measured after the first treatment on Day 7 of each treatment period; –, not calculated.

6.2.2.2 Foreign Phase I study in patients with renal impairment (CTD 5.3.3.3.1, Study 112 [to 20])

An open-label, uncontrolled study was conducted in 9 healthy adults and 16 patients with mild, moderate, and severe renal impairment (8, 3, and 5 subjects, respectively) to assess the PK, etc. of forodesine. Following a single oral dose of forodesine 100 mg, plasma and urinary forodesine concentrations were evaluated.

Table 10 shows the PK parameters of forodesine. The AUC_{last} in patients with mild, moderate, and

severe renal impairment was approximately 1.3, 1.5, and 1.8-fold that of the healthy adults. In contrast, no clear differences were noted in C_{max}. The urinary excretion rates of forodesine up to 168 hours following administration were 10.3% in healthy adults, 13.6% in patients with mild renal impairment, 8.2% in patients with moderate renal impairment, and 7.6% in patients with severe renal impairment.

Table 10. PK parameters of forodesine in healthy adults and patients with renal impairment

Severity of renal impairment[*1]	n	C_{max} (ng/mL)	t_{max}[*2] (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL/F (mL/min)
Normal	9	214 ± 134	3.00 (2.00, 48.0)	8949 ± 3228	63.0 ± 29.4	160 ± 59.8
Mild	8	248 ± 90.8	2.00 (2.00, 5.00)	11,640 ± 2457	40.3 ± 25.0	117 ± 40.5
Moderate	3	218 ± 72.6	5.00 (2.00, 6.00)	13,183 ± 2094	57.7 ± 9.79	97.2 ± 7.98
Severe	5	257 ± 115	4.00 (3.00, 12.0)	16,382 ± 2950	81.8 ± 62.0	73.4 ± 27.9

Mean ± standard deviation; [*1] normal, creatinine clearance (CrCL) >80 mL/min, mild; CrCL ≥50 mL/min and ≤80 mL/min; moderate, CrCL ≥30 mL/min and <50 mL/min; severe, CrCL <30 mL/min; [*2] median (range)

6.2.3 PPK analysis

A PPK analysis was performed by non-linear mixed-effects modeling (software program, NONMEM version 7.2.0) using forodesine PK data (209 subjects, 5298 measuring time points) obtained from Japanese clinical studies (Studies J01 and J02) and foreign clinical studies (Studies 105, BCX1777-Hio-05-107, BCX1777-111, 112, BCX1777-115, 116, 203, and 204). The PK of forodesine was described using a 2-compartment model with first-order elimination.

Potential covariates for (a) CL/F, (b) apparent central volume of distribution (Vc/F), and (c) absorption rate constant of forodesine were respectively (a) sex, meal condition, ideal body weight, CrCL, albumin, total bilirubin, AST, and alanine aminotransferase (ALT); (b) sex, ideal body weight, CrCL, AST, and ALT; and (c) sex, meal condition, race, and total bilirubin. As a result of the analysis, (a) CrCL was identified as the significant covariate for CL/F, and (b) ideal body weight for Vc/F.

The applicant's explanation about the results:

- The results showed that CL/F of forodesine in patients with CrCL of 50 and 30 mL/min would be lower than that in subjects with CrCL of 80 mL/min by 40.0% and 65.7%, respectively. The estimation is generally consistent with the decreased CL/F of forodesine in patients with deteriorating renal function observed in the foreign Phase I study (Study 112) [see Section "6.2.2.2 Foreign Phase I study in patients with renal impairment"].
- The C_{max} of forodesine in the patient with the lowest ideal body weight (36.2 kg) and the patient with the highest ideal body weight (86.0 kg) was estimated by the PPK analysis (940 and 808 ng/mL, respectively). Because of no clear difference between the values, ideal body weight is unlikely to give impact on the PK of forodesine that may pose clinical problems.

6.2.4 Relationship of forodesine exposure to efficacy and safety

Relationships of C_{min} to the safety and efficacy of forodesine were investigated using the results of the Japanese Phase I/II study (Study J02).

A relationship of C_{min} and response was studied. The results indicated no clear relationship between C_{min} of forodesine and response. A study on a relationship between C_{min} of forodesine and the incidence of Grade ≥3 adverse events also demonstrated no clear relationship.

6.2.5 Effects of hepatic impairment on the PK of forodesine

The applicant explained that hepatic impairment is unlikely to affect the PK of forodesine based on the following:

- It is suggested that hepatic metabolism is not a major route of elimination of forodesine [see Section "4.3 Metabolism"].
- In the PPK analysis, albumin, total bilirubin, ALT, and AST were not identified as significant covariates for the PK parameters of forodesine [see Section "6.2.3 PPK analysis"].
- In Study J02, no clear difference was observed between the PTCL patients with normal hepatic function and those with hepatic impairment[14)] in the incidence of adverse events.

6.2.6 Difference in PK of forodesine between Japanese and non-Japanese populations

The applicant explained that there are no clear differences in the PK of forodesine between Japanese and non-Japanese populations based on the following points:

- The results of the Japanese Phase I/II study (Study J02), and foreign Phase I study (Study 116) showed that there was no clear difference in the C_{max} and AUC of forodesine at steady state following oral dose of 300 mg BID between these studies [see Sections "6.2.1.2 Japanese Phase I/II study" and "6.2.2.1 Foreign Phase I study"].
- In the PPK analysis, race was not identified as a significant covariate for the PK parameters of forodesine [see Section "6.2.3 PPK analysis"].

6.R Outline of the review conducted by PMDA

6.R.1 Administration of forodesine to patients with renal impairment

The applicant's explanation about the administration of forodesine to patients with renal impairment:

In the foreign Phase I study (Study BCX1777-Hio-05-107), the urinary excretion rate of forodesine following intravenous administration was 91.0% [see Section "6.1.2.2 Foreign Phase I study"], which suggests that forodesine is eliminated mainly by renal excretion. In the foreign Phase I study (Study 112) conducted in patients with renal impairment, AUC_{last} increased with increasing severity of renal impairment [see Section "6.2.2.2 Foreign Phase I study in patients with renal impairment"]. These outcomes and the occurrence of adverse events in Studies J02 and 112 [see Section "7.R.5.2 Dose modifications for patients with renal impairment"] drew the following conclusions on the administration of forodesine to patients with renal impairment of different severity:

- No dose reduction is required for patients with mild or moderate renal impairment.
- Forodesine should be administered with caution to patients with moderate or severe renal impairment.

14) Patients who had screening AST or ALT equivalent to NCI-CTCAE Grade 1

- Dose reduction to 200 mg should be considered for patients with severe renal impairment.

PMDA's view:
The results of Study 112 suggested that patients with renal impairment have increased exposure to forodesine, and thus dose reduction should be considered before treating this patient population. During treatment, patient condition should be carefully monitored particularly for adverse events. The results of Study 112 should be communicated to healthcare professionals using the package insert, etc. in an appropriate manner.

The dose of forodesine for patients with renal impairment is unclear from a clinical pharmacological point of view, and it will be discussed based on the safety data of forodesine from the clinical studies [see Section "7.R.5.2 Dose modifications for patients with renal impairment"].

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

The applicant submitted the results from 2 Japanese clinical studies, a Phase I study and a Phase I/II study, as efficacy and safety evaluation data (Table 11). As reference data, the applicant submitted the results from 8 foreign clinical studies, 4 Phase I studies, 1 Phase I/II study, and 3 Phase II studies (Table 11).

Table 11. Clinical studies conducted to evaluate efficacy and safety

Data	Region	Study Identifier	Phase	Population	Number of subjects	Forodesine dosing regimen	Major endpoints
Evaluation	Japan	J01	I	Relapsed or refractory T/NK-cell tumor[*1]	13	100, 200, or 300 mg QD oral	Safety PK
		J02	I/II	Relapsed or refractory PTCL[*2]	48 (I) 4 (II) 44	300 mg BID oral	Efficacy Safety PK
Reference	Foreign	BCX1777-Hio-05-107	I	Healthy adults	18	Single dose 300 mg oral in the fasted state or after a meal; or single dose 40 mg/m^2 intravenous in the fasted state	Safety PK
		BCX1777-111	I	Healthy adults	36	Single dose 200 mg oral	Safety PK
		112	I	Healthy adults or patients with renal impairment	25	Single dose 100 mg oral	Safety PK
		116	I	Healthy adults	54	7-Day crossover regimens separated by a washout period of ≥7 days (a) 200 mg BID oral; 400 mg QD oral; and 40 mg/m^2 intravenous (b) 300 mg BID oral; 600 mg QD oral; and 40 mg/m^2 QD intravenous (c) 400 mg BID oral; 800 mg QD oral; and 40 mg/m^2 QD intravenous	Safety PK
		105	I/II	Relapsed or refractory CTCL	64	(a) Phase I: 40, 80, 160, or 320 mg/m^2 QD oral (b) Phase II: 80 mg/m^2 QD, oral; 300 mg QD oral; or 300 mg QD oral for 2 weeks followed by 2-week washout in repeated cycles	Safety PK
		203	II	Relapsed or refractory CTCL	144	200 mg QD oral	Efficacy Safety
		204	II	Relapsed or refractory chronic lymphocytic leukemia (CLL)	8	200 mg QD oral	Efficacy Safety
		210	II	CLL	33	200 mg QD or 200 mg BID oral	Efficacy Safety PK

[*1] According to the World Health Organization (WHO) classification (*J Clin Oncol*. 1999;17:3835-49); [*2] In Study J02, patients with ≥1 prior antineoplastic drug treatment who had aggravated symptoms after achieving partial remission (PR) or better to the most recent antineoplastic drug treatment.

The following sections summarize the clinical studies.

Major adverse events observed in the studies except for deaths are described in Section "7.3 Adverse events in clinical studies," and study results related to PK in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods," and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Japanese Phase I study (CTD 5.3.3.2.1, Study J01 [January 2009 to July 2013])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory T/NK-cell tumors except T-ALL/T-LBL (target sample size, 3-24 subjects) at 4 centers in Japan to investigate the safety, tolerability, and PK of forodesine.

Subjects received oral forodesine 100, 200, or 300 mg QD until disease progression or the treatment discontinuation criteria met.

All 13 subjects enrolled in the study and received forodesine (5 in the 100 mg group, 3 in the 200 mg group, and 5 in the 300 mg group) were included in the safety analysis set.

Dose limiting toxicity (DLT) was assessed through Day 28 of treatment. DLT was not observed in any of the groups, and the maximum tolerated dose (MTD) was not reached.

The safety results showed no deaths during the forodesine treatment period or within 30 days after the end of treatment.

7.1.1.2 Japanese Phase I/II study (CTD 5.3.5.2.1, Study J02 [ongoing since January 2013, data cut-off on August 3, 2015])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory PTCL[13)] (target sample size, 3-6 subjects in Phase I and 43 subjects in Phase II) at 21 centers in Japan to investigate the efficacy and safety, etc. of forodesine.

Subjects received forodesine 300 mg BID until disease progression or the treatment discontinuation criteria met.

All 48 subjects enrolled in the study (4 in Phase I, and 44 in Phase II) received forodesine and were included in the safety analysis set. Of these, 3 subjects did not meet the inclusion criteria,[15)] and the remaining 45 subjects (4 in Phase I, and 41 in Phase II) were included in the efficacy analysis set.

15) Two subjects were determined by the central pathology review to have tissue type not specified in the protocol (one with plasmablastic lymphoma and the other with follicular dendritic cell sarcoma), and 1 subject did not have evaluable target lesions.

The efficacy primary endpoints of the study were the best overall response and the response rates in Phase II[16] determined by the central review according to the Revised Response Criteria for Malignant Lymphoma (Revised RC) (*J Clin Oncol.* 2007;25:579-86). The results are shown in Table 12.

Table 12. Best overall response and response rates (central review, efficacy analysis set for Phase II, data cut-off on August 3, 2015)

Best overall response	Number of subjects (%) 41
Complete remission (CR)	4 (9.8)
Partial remission (PR)	5 (12.2)
Stable disease (SD)	7 (17.1)
Progressive disease PD	24 (58.5)
Not evaluable (NE)	1 (2.4)
Responded (CR + PR)	9
Response rate (%) (90% CI)* (%)	22.5 (12.0-35.3)

* Uniformly minimum variance unbiased estimator (*Statist Med.* 2004;23:881-96)

The safety results showed that during forodesine treatment or within 30 days after the end of treatment, 1 in 48 subjects (2.1%) died due to disseminated intravascular coagulation/multi-organ failure. A causal relationship to forodesine was ruled out for the event.

7.2 Reference data

7.2.1 Clinical pharmacology studies

The following 4 clinical pharmacology studies were conducted in healthy adults and patients with renal impairment, and their results were submitted [see Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology"]. There were no deaths during the study period[17] of these studies.

7.2.1.1 Foreign Phase I study (CTD 5.3.1.1.1, Study BCX1777-Hio-05-107 [[redacted] to [redacted])

7.2.1.2 Foreign Phase I study (CTD 5.3.1.2.1, Study BCX1777-111 [[redacted] to [redacted])

7.2.1.3 Foreign Phase I study (CTD 5.3.3.3.1, Study 112 [[redacted] to [redacted])

7.2.1.4 Foreign Phase I study (CTD 5.3.4.1.1, Study 116 [[redacted] to [redacted])

7.2.2 Foreign clinical studies

7.2.2.1 Foreign Phase I/II study (CTD 5.3.4.2.1, Study 105 [[redacted] to [redacted])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory CTCL (target sample size, 52-72 subjects) at 11 centers outside Japan to investigate the safety and tolerability, etc. of

16) The threshold response rate was specified as 10%, based on 9%, the lower limit of the proportion of response at the 95% CI in the results from clinical studies of other antineoplastic drugs (romidepsin [unapproved in Japan], gemcitabine hydrochloride, belinostat [unapproved in Japan], lenalidomide hydrate, pralatrexate [unapproved in Japan], and denileukin diftitox [unapproved in Japan]) when administered alone in patients with relapsed or refractory PTCL (*Blood.* 2011;117:5827-34, *Ann Oncol*. 2010;21:860-3, *Blood.* 2009;114:920, *Cancer.* 2010;116:4541-8, *J Clin Oncl.* 2011;29:1182-9, and *Br J Haematol.* 2007;136:439-47). Simon's (mini-max) 2-stage designs were used with a prespecified threshold response rate of 10%, an expected response rate of 25%, a 1-tailed significance level of 5%, and a statistical power of 80%. The study was to proceed to the second stage when ≥3 out of 22 subjects responded at the first stage. The efficacy of treatment was to be demonstrated by the response of ≥ 8 out of 40 subjects.

17) Studies 107 and 111, during the forodesine treatment period or within 21 days after the end of treatment; Study 112, during the forodesine treatment period or within 10 days after the end of treatment; Study 116, during the forodesine treatment period or within 41 days after the end of treatment.

forodesine.

All 64 subjects enrolled in the study received forodesine, and were included in the safety analysis set.

The safety results showed that 1 in 64 subjects (1.6%) died due to disease progression during treatment or within 30 days after the end of treatment. A causal relationship to forodesine was ruled out for the event.

7.2.2.2 Foreign Phase II study (CTD 5.3.5.4.1, Study 203 [20 to 20])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory CTCL (target sample size, 100 subjects) at 37 centers outside Japan to investigate the efficacy and safety of forodesine.

All 144 subjects enrolled in the study received forodesine and were included in the safety analysis set.

The safety results showed that 6 in 144 subjects (4.2%) died due to septic shock (2 subjects), infection, sepsis, oesophageal carcinoma, and mycosis fungoides (1 subject each) during treatment or within 30 days after the end of treatment. A causal relationship to forodesine could not be ruled out for sepsis.

7.2.2.3 Foreign Phase II study (CTD 5.3.5.4.2, Study 204 [20 to 20])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory CLL (target sample size, 30 subjects) at 1 center outside Japan to investigate the efficacy and safety of forodesine.

All 8 subjects enrolled in the study received forodesine and were included in the safety analysis set.

The safety results showed that 2 in 8 subjects (25.0%) died during treatment or within 30 days after the end of treatment. The causes of death were abdominal pain and cardiopulmonary failure (1 subject each), and a causal relationship to forodesine was ruled out for both events.

7.2.2.4 Foreign Phase II study (CTD 5.3.5.4.3, Study 210 [20 to 20])

An open-label, uncontrolled study was conducted in patients with untreated, relapsed or refractory CLL, or untreated CLL not suitable for standard therapies[18)] (target sample size, 26 subjects) at 9 centers outside Japan to investigate the efficacy and safety of forodesine.

All 33 subjects enrolled in the study received forodesine and were included in the safety analysis set.

The safety results showed that 2 of 33 subjects (6.1%) died during the forodesine treatment period or within 30 days after the end of treatment. The causes of death were autoimmune thrombocytopenia/haemorrhage intracranial and septic shock/pneumonia/respiratory failure (1 subject

[18] Patients meeting ≥1 of the following criteria: age of ≥66 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 or 3; or intolerance to standard chemotherapies determined by the doctor.

each), and a causal relationship to forodesine was ruled out for both events.

7.R Outline of the review conducted by PMDA

7.R.1 Review policy

PMDA considered the Japanese Phase I/II study conducted in patients with relapsed or refractory PTCL (Study J02) as the pivotal study in evaluating the efficacy and safety of forodesine among the evaluation data submitted, and decided to evaluate based mainly on Study J02.

7.R.2 Efficacy

PMDA concluded that the efficacy of forodesine in the treatment of relapsed or refractory PTCL was demonstrated by the following review results.

7.R.2.1 Efficacy endpoints and results of efficacy evaluation

The applicant's view on the primary endpoints and the efficacy of forodesine in patients with relapsed or refractory PTCL in Study J02:

The prognosis for patients with relapsed or refractory PTCL is unfavorable, and there is no established standard therapy that is expected to improve overall survival (OS). Patients' response to the treatment is of clinically significant and, therefore, response rate is the appropriate primary endpoint of Study J02.

According to the protocol of the Phase II of Study J02, the study treatment was rated as effective by response of ≥8 subjects. Because 9 subjects responded [see Section "7.1.1.2 Japanese Phase I/II study"], the efficacy of forodesine in the treatment of relapsed or refractory PTCL was demonstrated.

PMDA's view:

The applicant's explanation about the endpoint in view of the clinical significance of response of patients with relapsed or refractory PTCL is acceptable. Based on the above results, etc., the efficacy of forodesine in the treatment of relapsed or refractory PTCL was demonstrated.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events in clinical studies"]

Based on the reviews in the following subsections, PMDA considers that treatment with forodesine in patients with relapsed or refractory PTCL require particular attention to hematotoxicity, infections, and secondary malignancy. Vigilance should be exercised for the onset of these adverse events.

Furthermore, peripheral nerve disorder, skin disorder, and cardiac failure are of particular attention. PMDA however concluded that forodesine is tolerated in patients when they are followed by a physician with adequate knowledge and experience in the treatment of hematopoietic malignancies by appropriate means including monitoring and control of adverse events, dose interruption or reduction, and treatment discontinuation.

7.R.3.1 Safety profile of forodesine

The applicant's explanation about the safety profile of forodesine based on the safety data from Study

J02:

Table 13 summarizes the safety data from Study J02.

Table 13. Summary of safety data (Study J02)

	Number of subjects (%) 48
All adverse events	48 (100)
Grade ≥3 adverse events	46 (95.8)
Adverse events resulting in death	1 (2.1)
Serious adverse events	19 (39.6)
Adverse events leading to treatment discontinuation	7 (14.6)
Adverse events leading to treatment interruption	14 (29.2)
Adverse events leading to dose reduction	1 (2.1)

In Study J02, adverse events with an incidence of ≥10% were lymphocyte count decreased (100%, 48 of 48 subjects), white blood cell count decreased (72.9%, 35 of 48), neutrophil count decreased (54.2%, 26 of 48), platelet count decreased (45.8%, 22 of 48), anaemia (41.7%, 20 of 48), nasopharyngitis (25.0%, 12 of 48), hypoalbuminaemia (25.0%, 12 of 48), constipation (25.0%, 12 of 48), headache (22.9%, 11 of 48), insomnia (20.8%, 10 of 48), pyrexia (20.8%, 10 of 48), ALT increased (20.8%, 10 of 48), stomatitis (18.8%, 9 of 48), nausea (16.7%, 8 of 48), rash (16.7%, 8 of 48), AST increased (16.7%, 8 of 48), herpes zoster (14.6%, 7 of 48), decreased appetite (14.6%, 7 of 48), pruritus (14.6%, 7 of 48), malaise (14.6%, 7 of 48), oedema (14.6%, 7 of 48), urinary protein positive (14.6%, 7 of 48), vomiting (12.5%, 6 of 48), hepatic function abnormal (12.5%, 6 of 48), CMV infection (10.4%, 5 of 48), pneumonia (10.4%, 5 of 48), febrile neutropenia (10.4%, 5 of 48), hyponatraemia (10.4%, 5 of 48), oedema peripheral (10.4%, 5 of 48). Grade ≥3 adverse events that occurred in ≥2 subjects were lymphocyte count decreased (95.8%, 46 of 48), white blood cell count decreased (41.7%, 20 of 48), neutrophil count decreased (33.3%, 16 of 48), platelet count decreased (25.0%, 12 of 48), anaemia (20.8%, 10 of 48), febrile neutropenia (10.4%, 5 of 48), pneumonia (8.3%, 4 of 48), hyponatraemia (8.3%, 4 of 48), decreased appetite (6.3%, 3 of 48), hypoalbuminaemia (4.2%, 2 of 48), diarrhoea (4.2%, 2 of 48), hepatic function abnormal (4.2%, 2 of 48), rash maculo-papular (4.2%, 2 of 48). Serious adverse events that occurred in ≥2 subjects were pneumonia (8.3%, 4 of 48) and pyrexia (6.3%, 3 of 48). Adverse events leading to dose interruption in ≥2 subjects were nasopharyngitis (6.3%, 3 of 48), neutrophil count decreased (4.2%, 2 of 48), herpes zoster (4.2%, 2 of 48), pneumonia (4.2%, 2 of 48), and rash maculo-papular (4.2%, 2 of 48). No adverse events led to treatment discontinuation or dose reduction in ≥2 subjects.

PMDA's view:

The use of forodesine requires vigilance for frequent, serious or Grade ≥3 adverse events observed in Study J02. The occurrence of these events should be communicated to healthcare professionals in an appropriate manner. Due to the extremely limited safety data of forodesine, post-marketing safety data need to be collected. New findings should be communicated to healthcare professionals promptly.

In the following subsections, PMDA focuses on Grade ≥3 or serious adverse events for which a causal

relationship to forodesine could not be ruled out and frequent Grade ≥3 or serious adverse events, primarily based on the safety results from Study J02.

7.R.3.2 Hematotoxicity

The applicant explained about the occurrence of hematotoxicity following administration of forodesine: Hematotoxicity-related adverse events were tabulated by preferred term (PT) falling under the Medical Dictionary for Regulatory Activities (MedDRA) standard MedDRA queries (SMQ) (Medical Dictionary for Regulatory Activities Japanese version [MedDRA/J] ver.18.1) of "hematopoietic cytopenias."

Table 14 shows the occurrence of hematotoxicity in Study J02.

Table 14. Occurrence of hematotoxicity (Study J02)

PT (MedDRA/J ver.18.1)	Number of subjects (%) 48	
	All Grades	Grade ≥3
Hematotoxicity	48 (100)	46 (95.8)
Lymphocyte count decreased	48 (100)	46 (95.8)
White blood cell count decreased	35 (72.9)	20 (41.7)
Neutrophil count decreased	26 (54.2)	16 (33.3)
Platelet count decreased	22 (45.8)	12 (25.0)
Anaemia	20 (41.7)	10 (20.8)
Febrile neutropenia	5 (10.4)	5 (10.4)
Bone marrow failure	1 (2.1)	1 (2.1)

In Study J02, there was no hematotoxicity resulting in death. Serious hematotoxicity occurred in 1 of 48 subjects (2.1%, anaemia), and its causal relationship to forodesine could not be ruled out. Hematotoxicity led to dose interruption in 2 of 48 subjects (4.2%, neutrophil count decreased [2] and white blood cell count decreased [1] [a subject had >1 event]). A causal relationship to forodesine could not be ruled out for neutrophil count decreased in 1 subject. There was no hematotoxicity leading to treatment discontinuation or dose reduction.

PMDA's view:

In Study J02, Grade ≥3 hematotoxicity was caused by forodesine frequently and a causal relationship to forodesine could not be ruled out for a serious hematotoxicity. Therefore, attention should be paid to forodesine-induced hematotoxicity during treatment. The occurrence of hematotoxicity in Study J02 must be communicated to healthcare professionals through the package insert, etc. in an appropriate manner. The package insert should also remind of the importance of a hematological test performed on a regular basis and appropriate actions for detected abnormality including dose interruption or reduction and blood transfusion.

7.R.3.3 Infections

The applicant's explanation about the occurrence of infections following administration of forodesine: Infection-related adverse events were tabulated by PT falling under MedDRA system organ class (SOC)

(MedDRA/J ver.18.1) of "infections and infestations."

Table 15 shows the incidences of infections occurring in ≥2 subjects in Study J02.

Table 15. Occurrence of infections in ≥2 subjects (Study J02)

PT (MedDRA/J ver.18.1)	Number of subjects (%) 48	
	All Grades	Grade ≥3
Infections	29 (60.4)	6 (12.5)
Nasopharyngitis	12 (25.0)	0
Herpes zoster	7 (14.6)	1 (2.1)
Pneumonia	5 (10.4)	4 (8.3)
CMV infection	5 (10.4)	0
Upper respiratory tract infection	4 (8.3)	0
Bronchitis	2 (4.2)	1 (2.1)
Genital herpes	2 (4.2)	0
Oral candidiasis	2 (4.2)	0

In Study J02, there were no fatal infections. Serious infections occurred in 7 of 48 subjects (14.6%; pneumonia [4 subjects], pneumocystis jirovecii pneumonia, pneumonia bacterial, gastrointestinal infection, upper respiratory tract infection, sinusitis fungal, gastroenteritis, bronchitis, and herpes zoster meningitis [1 each] [subjects may have had >1 event]), and a causal relationship to forodesine could not be ruled out for any of these events. Infections led to treatment discontinuation in 2 of 48 subjects (4.2%; herpes zoster and pneumonia [1]), and a causal relationship to forodesine could not be ruled out for either any of these events. Infections led to dose interruption in 7 of 48 subjects (14.6%; nasopharyngitis [3], pneumonia and herpes zoster [2 each], gastrointestinal infection, upper respiratory tract infection, pneumocystis jirovecii pneumonia, sinusitis fungal, influenza, and bronchitis [1 each] [subjects may have had >1 event]), and a causal relationship to forodesine could not be ruled out for any of these events except nasopharyngitis in 1 subject. Infection led to dose reduction in 1 of 48 subjects (2.1%; pneumonia), and its causal relationship to forodesine could not be ruled out.

In Study J02, sulfamethoxazole-trimethoprim, antiherpesvirus agent, etc. were allowed to be used with forodesine for the prevention of infection. PMDA asked the applicant to explain about (a) the occurrence of opportunistic infections and hepatitis B virus (HBV) reactivation associated with forodesine and (b) prophylactic medication for infections and virus marker monitoring performed in Study J02. Further, PMDA asked the applicant's views about whether cautionary advice on infections associated with forodesine treatment should be given.

The applicant's explanation:

(a)

Infections observed in the study other than those listed in Table 15 were herpes zoster meningitis, herpes simplex, herpes zoster disseminated, pneumocystis jirovecii pneumonia, and HBV reactivation (1 each; subjects may have had >1 event). There were no fatal infections. Serious adverse events occurred in 2 of 48 subjects (4.2%; pneumocystis jirovecii pneumonia and herpes zoster meningitis [1 each]), and a

causal relationship to forodesine could not be ruled out for either event.

(b)

- HBV: At the pre-inclusion screening, HBs antigen positive patients, or HBs- or HBc-antibody-positive patients were excluded if their HBV-deoxyribonucleic acid (DNA) quantification was greater than the detectable sensitivity. After the start of forodesine treatment, subjects were monitored on a regular basis in accordance with the "Guideline for the Prevention of Immunosuppressive Therapy or Chemotherapy-induced Reactivation of Hepatitis B Virus Infection (revised version)" (The Japan Society of Hepatology). HBV reactivation occurred in 1 of 48 subjects (2.1%, hepatitis B DNA assay positive), and it resolved following an antiviral drug therapy.
- Cytomegalovirus (CMV): At the pre-inclusion screening, CMV antigen-positive patients (tested by CMV antigenemia assay) were excluded from the study. After the start of forodesine treatment, while no periodic monitoring was required, CMV antigen testing was performed. CMV-infected subjects were to be treated with an antiviral drug at the physician's discretion. A total of 5 of the 48 subjects (10.4%) suffered CMV infection. Of these, 2 subjects recovered and 3 remained unresolved after an antiviral drug therapy.
- Mycobacterium tuberculosis: There was no pre-inclusion screening or regular monitoring. No tuberculosis-related adverse events were observed.
- Infections with herpes simplex and herpes zoster viruses: Use of prophylactic antiviral drugs was allowed at the physician's discretion. A total 27 of the 48 subjects (56.3%) received a prophylactic antiviral drug. Herpes virus infection occurred in 10 of the 48 subjects (20.8%; herpes zoster [7], genital herpes [2], herpes zoster disseminated, herpes zoster meningitis, and herpes simplex [1 each] [subjects may have had >1 event]). The infections occurred in 4 of the 27 subjects (14.8%) who had received prophylaxis, and 6 of 21 subjects (28.6%) who did not receive prophylaxis. All 4 subjects with prophylaxis and 3 subjects without prophylaxis recovered, while the other 3 without prophylaxis remained unrecovered.

The above observations indicate a possible risk of infection including reactivation of HBV and CMV. Therefore, cautionary advice must be given in the package insert or relevant documents. Healthcare professionals should be advised to keep monitoring patients for a virus marker during and after forodesine treatment and take appropriate actions for abnormality detected, if any.

PMDA's view:

In the main, PMDA accepted the applicant's explanation. However, because of the observed serious infections for which a causal relationship to forodesine could not be ruled out, the occurrence of infections in Study J02 should be communicated to healthcare professionals through the package insert, etc. in an appropriate manner. Healthcare professionals should also be provided appropriately with written information about (a) specifications on the safety measures for HBV reactivation taken in Study J02, such as periodic virus marker monitoring and (b) safety measures actually taken by physicians in Study J02 for herpes simplex, herpes zoster, CMV infection, pneumocystis jirovecii pneumonia, and

other infections, for which no specific safety advice had been given and physicians were able to decide to take any effective measures including prophylactic medication.

7.R.3.4 Secondary malignancies

The applicant's explanation about the secondary malignancies associated with forodesine treatment:

Secondary malignancy-related adverse events were tabulated by PT under the MedDRA SMQ (MedDRA/J ver.18.1) of "malignant tumours." Events indicative of worsening of underlying diseases were excluded.[19)]

Table 16 shows details of patients who had secondary malignancies in Study J02.

Table 16. List of patients who had secondary malignancies (Study J02)

Age	Sex	Histopathological type	PT (MedDRA/J ver.18.1)	Grade	Seriousness	Onset (Day)	Causal relationship	Outcome
7[redacted]	F	AITL	EBV-associated lymphoma	3	Serious	450	Y	Not resolved
7[redacted]	M	PTCL-NOS	Blast cell crisis	3	Non-serious	11	N	Not resolved
			Acute myeloid leukaemia	4	Serious	18	N	Not resolved
7[redacted]	F	AITL	EBV-associated lymphoma	3	Serious	203	Y	Not resolved
7[redacted]	F	AITL	EBV-associated lymphoma	–[*1]	Serious	435[*2]	Y	Death
5[redacted]	M	AITL	Myelodysplastic syndrome	4	Serious	631[*2]	Y	Not resolved
7[redacted]	F	PTCL-NOS	EBV-associated lymphoma	3	Serious	280	Y	Death
6[redacted]	F	PTCL-NOS	DLBCL	3	Serious	505	Y	Not resolved
6[redacted]	M	AITL	Gastric cancer	–[*1]	Serious	1108	Y	Not resolved

M, male; F, female

[*1] The grade was not given in the adverse drug reaction report. [*2] The patients were receiving post-treatment because of worsening of the underlying disease

In Study J02, secondary malignancies led to treatment discontinuation in 5 of 48 subjects (10.4%; Epstein-Barr virus (EBV)-associated lymphoma [2 subjects], acute myeloid leukaemia, diffuse large B cell lymphoma (DLBCL), and gastric cancer [1 each]). A causal relationship to forodesine could not be ruled out for the events in 4 subjects except acute myeloid leukaemia. There were no secondary malignancies leading to dose interruption or dose reduction.

EBV-associated lymphoma resulted in death of 2 of 4 affected subjects in Study J02. In immunosuppressed patients, EBV reactivation induces the proliferation of EBV-infected B-cells resulting in tumor formation (*The Journal of the Japanese Society of Internal Medicine.* 2001;90:94-9). Monitoring of patients should be continued during and after the forodesine treatment, and detected abnormality, if any, must be appropriately treated.

There were limited number of subjects experiencing secondary malignancies in the Japanese clinical studies. PMDA asked the applicant to explain the occurrence of secondary malignancies in the foreign clinical studies (Studies 105, 203, 204, and 210) on the understanding that the indications and regimens in the foreign studies differ from those proposed for the current application.

[19)] The data include new secondary malignancies reported on and after the data cut-off date (August 3, 2015) until December 9, 2016.

The applicant's explanation:
In the foreign clinical studies listed above, secondary malignancies occurred in 17 of 249 subjects (6.8%; squamous cell carcinoma [7], basal cell carcinoma [4], DLBCL [2], squamous cell carcinoma of skin, lymphoma cutis, glioblastoma, lung neoplasm, lung adenocarcinoma, and oesophageal carcinoma [1 each] [subjects may have had >1 event]). A causal relationship to forodesine could not be ruled out for the events in 6 subjects (DLBCL [2], glioblastoma, lung neoplasm, squamous cell carcinoma of skin, and squamous cell carcinoma [1 each]).

Given that a causal relationship to forodesine could not be ruled out for fatal secondary malignancies both in the Japanese and foreign clinical studies, the occurrence of secondary malignancies should be communicated to healthcare professionals using the package insert, etc. in an appropriate manner.

PMDA's view:
In the main, PMDA accepted the applicant's explanation. However, there were limited number of patients enrolled in Study J02 and patients experiencing secondary malignancies including EBV-associated lymphoma. This precludes a firm conclusion about forodesine-induced secondary malignancies. Data on the occurrence of secondary malignancies should be provided to healthcare professionals using the package insert, etc. in an appropriate manner. During continued data collection, new findings should be communicated to healthcare professionals.

7.R.3.5 Other
In this section, PMDA focuses on (a) peripheral nerve disorders (b) and skin disorders, which were reported as Grade ≥3 from >1 subjects in Study J02 albeit their low incidences, and (c) cardiac failure, which is a potential concern in the use of forodesine identified in foreign clinical studies (Studies 105, 203, 204, and 210) in patients with hematopoietic malignancies.

The applicant's explanation:
(a) Peripheral nerve disorders
PTs under the MedDRA SMQ (MedDRA/J ver.18.1) of "peripheral neuropathy" were tabulated. In Study J02, peripheral nerve disorder occurred in 7 of 48 subjects (14.6%). A serious peripheral nerve disorder occurred in 1 of 48 subjects (2.1%; muscular weakness), and a causal relationship to forodesine could not be ruled out for the event. Grade ≥3 peripheral nerve disorders occurred in 2 of 48 subjects (4.2%; muscular weakness and peripheral sensory neuropathy [1 each]), and a causal relationship to forodesine could not be ruled out for either events. No peripheral nerve disorders resulted in death.
(b) Skin disorders
PTs under the MedDRA SOC (MedDRA/J ver.18.1) of "skin and subcutaneous tissue disorders" were tabulated. In Study J02, skin disorders occurred in 25 of 48 subjects (52.1%). Grade ≥3 skin disorders occurred in 3 of 48 subjects (6.3%; rash maculo-papular [2], erythema multiforme, pustular psoriasis, and skin ulcer [1 each]) [subjects may have had >1 event]). A causal relationship

to forodesine could not be ruled out for rash maculo-papular, erythema multiforme, and pustular psoriasis in 1 subject each. No serious or fatal skin disorders were reported.

(c) Cardiac failure

PTs under the MedDRA SMQ (MedDRA/J ver.18.1) of "cardiac failure" were tabulated. In Study J02, cardiac failure occurred in 1 of 48 subjects (2.1%; cardiac failure acute), and a causal relationship to forodesine was ruled out for the event. In the foreign clinical studies (Studies 105, 203, 204, and 210), cardiac failure occurred in 9 of 249 subjects (3.6%; cardiac failure congestive [5], pulmonary oedema [2], cardiac failure and cardiopulmonary failure [1 each]). Fatal cardiac failure occurred in 1 of 249 subjects (0.4%; cardiopulmonary failure), and a causal relationship to forodesine was ruled out for the event. Serious cardiac failure occurred in 6 of 249 subjects (2.4%; cardiac failure congestive [5] and cardiopulmonary failure [1]). A causal relationship to forodesine could not be ruled out for cardiac failure congestive in 2 subjects.

PMDA's view:

There were limited number of subjects and those who experienced peripheral nerve disorder and skin disorder in Study J02, and this precludes a firm conclusion at present on the occurrence of peripheral nerve disorder and skin disorder associated with forodesine treatment. However, given that a causal relationship to forodesine could not be ruled out for >1 serious adverse events and Grade ≥3 adverse events observed in the study, the use of forodesine requires vigilance against peripheral nerve disorders and skin disorders. The occurrence of these events should be communicated to healthcare professionals through the package insert, etc. in an appropriate manner.

A causal relationship to forodesine was ruled out for the serious cardiac failure observed in Study J02, and this precludes a firm conclusion on cardiac failure associated with forodesine treatment. However, a causal relationship to forodesine could not be ruled out for >1 serious cardiac failure observed in the foreign clinical studies (Studies 105, 203, 204, and 210). The use of forodesine thus requires vigilance against cardiac failure, and the occurrence of relevant events in the foreign clinical studies should be communicated to healthcare professionals using written materials.

7.R.4 Clinical positioning and indication

In the application for marketing approval, the proposed indication for forodesine was "relapsed or refractory peripheral T-cell lymphoma." The applicant also included the following statements in the "Precautions for indication" section:

- Forodesine should be used only in patients who have PTCL confirmed by pathology test.
- Treating physicians must determine if the patient is suitable for the treatment with forodesine based on a good knowledge from the "Clinical studies" section, such as the histopathological types of the patients enrolled in the clinical studies and adequate understanding of the efficacy and safety of forodesine, and after due consideration of the feasibility of other options than forodesine.

Based on the discussions in Sections "7.R.2 Efficacy" and "7.R.3 Safety," and in the following

subsections, PMDA concluded that the indication for forodesine should be "relapsed or refractory peripheral T-cell lymphoma," as per the proposal, and that the "Clinical studies" section in the package insert should note the histopathological types of the subjects enrolled in Study J02 and the "Precautions for indication" section the following advice:

- A disease to be treated with forodesine should be confirmed by physicians or at medical centers with adequate experience in pathological diagnosis.
- Treating physicians must determine if the patient is suitable for the use of forodesine based on a good knowledge from the "Clinical studies" section, such as the histopathological types of patients enrolled in the clinical studies, and adequate understanding of the efficacy and safety of forodesine.

7.R.4.1 Clinical positioning and intended patient population of forodesine

There are no Japanese or foreign clinical practice guidelines[20] or major international clinical oncology and hematology textbooks[21] referring to forodesine in the treatment of relapsed or refractory patients with PTCL.

PMDA asked the applicant to explain the clinical positioning of forodesine in treatment for patients with relapsed or refractory PTCL and the intended patient population of forodesine.

The applicant's explanation:

Because of the efficacy of forodesine in the treatment of relapsed or refractory PTCL demonstrated in Study J02, forodesine deserves to be a therapeutic option for the intended patient population. Table 17 shows best overall response and the response rates in Study J02 by histopathological type determined by the central review according to Revised RC (*J Clin Oncol*. 2007;25:579-86). Patients with the histopathological types of PTCL-not otherwise specified (NOS) and angioimmunoblastic T cell lymphoma (AITL) responded to forodesine, and therefore forodesine is expected to provide clinical benefit to patients with these types of PTCL.

Table 17. Best overall response and the response rates by histopathological type (Study J02, central review, efficacy analysis set [Phases I + II], data cut-off on August 3, 2015)

Histopathological type	Number of subjects (%) 45	Best overall response (number of subjects)					Number of responded (CR + PR) subjects (Response rate, %)
		CR	PR	SD	PD	NE	
PTCL-NOS	22 (48.9)	2	2	5	12	1	4 (18.2)
AITL	18 (40.0)	2	4	2	9	1	6 (33.3)
ALK-negative ALCL	2 (4.4)	0	0	0	2	0	0
ALK-positive ALCL	1 (2.2)	0	0	0	1	0	0
Extranodal NK/T-cell lymphoma, nasal type	1 (2.2)	0	0	0	1	0	0
Transformed mycosis fungoides*	1 (2.2)	0	0	0	1	0	0

* Transformed mycosis fungoides was defined as mycosis fungoides associated with pathological cell growth to form masses.

[20] *NCCN Guidelines* (v.3.2016), *ESMO Clinical Practice Guidelines* (*Ann Oncol.* 2015:26 suppl 5:v108-115), and *The Hematopoietic Tumor Guidelines* 2013 [in Japanese] (ed. by the Japanese Society of Hematology).

[21] *New Clinical Oncology*, 4th revised, ed. by Japanese Society of Medical Oncology [in Japanese] (Nankodo, 2015), *Wintrobe's Clinical Hematology,* 13th ed. (Lippincott Williams & Wilkins, 2014, USA), *Williams Hematology*, 9th ed. (the McGraw-Hill Companies, Inc. 2016, USA), and *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology,* 10th ed. (Lippincott Williams & Wilkins, 2014, USA)

Based on the following observations, forodesine may be used in patients who did not response to the treatment in Study J02 despite their histopathological types of PTCL eligible for the study (anaplastic lymphoma kinase [ALK]-positive anaplastic large cell lymphoma [ALCL]; ALK-negative ALCL; extranodal NK/T-cell lymphoma, nasal type; or transformed mycosis fungoides), patients with a histopathological type ineligible for Study J02 (enteropathy-associated T-cell lymphoma, hepatosplenic T-cell lymphoma, or subcutaneous panniculitis-like T-cell lymphoma), and patients who have not achieved PR or better to the most recent antineoplastic drug and thus who were ineligible for Study J02.

- Forodesine's PNP inhibitory effect promotes dGTP accumulation in T-cell derived malignant tumor cells and induces apoptosis, and is expected to have antiproliferative effect against PTCL, one of T cell-derived malignancy [see Section "3.R.1 Mechanism of action of forodesine and its efficacy against PTCL"].
- Because the efficacy of forodesine was demonstrated in patients with PTCL-NOS and AITL, forodesine is expected to have efficacy in patients with a PTCL histopathological type eligible for Study J02 but not responding to the treatment.

Based on the above, the "Clinical studies" section of package insert highlights that Study J02 was conducted in subjects who had relapsed symptoms after achieving PR or better to the most recent antineoplastic drug treatment, with the histopathological types eligible for the study and the efficacy results by histopathological type. The "Precautions for indication" section advises treating physicians to have a good knowledge from the "Clinical studies" section and adequate understanding of the efficacy and safety of forodesine before determining if the patient is suitable for the treatment. Given these, the indication was proposed as "relapsed or refractory peripheral T-cell lymphoma."

Mogamulizumab (genetical recombination) (referred to as mogamulizumab) and brentuximab vedotin (genetical recombination) (referred to as brentuximab) have already been approved for the treatment of relapsed or refractory PTCL. However, there are no clinical study data that compare safety and efficacy between forodesine and these approved drugs, and therefore, how to select the most appropriate one is unclear up to now. A suitable drug should be selected according to the patient's condition based on the mechanisms of action of these drugs.

PMDA's view:

In the main, PMDA accepted the applicant's explanations about the clinical positioning of forodesine and the intended patient population for forodesine, based on the following observation:

- There are no other therapies that are expected to prolong OS of patients with PTCL, and patients of all histopathological types are treated with forodesine in the same manner [see Section "7.R.4.1 Clinical positioning and intended patient population of forodesine"].
- In light of the extremely small number of patients with PTCL, there is difficulty designing clinical studies to assess the efficacy, etc. of forodesine for each histopathological type.
- Forodesine is meant to be prescribed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

PMDA further accepted the applicant's explanations about the indication in the main, agreeing to the proposed indication of "relapsed or refractory peripheral T-cell lymphoma." Meanwhile, there is a suggestion that the pathological diagnosis of PTCL should require histopathological type identification based on assessment by a hematopathologist in (*J Clin Oncol.* 2008;26:4124-30, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas [NCCN Guidelines]). Accordingly, PMDA concluded that the "Clinical studies" section of the package insert must indicate the histopathological types that were eligible for Study J02, along with reminders added in the "Precautions for indication" section to the effect that:

- A disease to be treated with forodesine should be confirmed by physicians or at medical centers with adequate experience in pathological diagnosis.
- Treating physicians must determine if the patient is suitable for the use of forodesine based on a good knowledge from the "Clinical studies" section, such as the histopathological types of patients enrolled in the clinical studies, and adequate understanding of the efficacy and safety of forodesine.

7.R.5 Dosage and administration

The proposed dosage and administration of forodesine was "The usual adult dosage is 300 mg of oral forodesine administered twice daily. The dose should be reduced according to the patient's condition." The "Precautions for dosage and administration" section had statements about the following:

- Dose modifications for patients with renal impairment
- Guidelines for dose interruption or other advice in case of an adverse drug reaction
- The efficacy and safety of forodesine used with other antineoplastic drugs have not been established.

Based on the discussions in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the following subsections, PMDA concluded that the dosage and administration of forodesine should be defined as per the applicant's proposal. Based on the discussion in Section "6.R.1 Administration of forodesine to patients with renal impairment" and the following subsections, PMDA further concluded that the "Precautions for dosage and administration" section should note the following:

- The efficacy and safety of forodesine used with other antineoplastic drugs have not been established.
- Patients with renal impairment are known to have high blood forodesine concentration. Patients in this population may be treated with a reduced dose, and their condition should be particularly carefully monitored for a sign of an adverse event.
- When forodesine causes any adverse drug reaction, corrective measures such as dose interruption may be taken according to the following criteria.

Criteria for dose interruption, dose reduction, and treatment discontinuation of forodesine

Adverse drug reaction*	Measures
Grade ≥3 non-hematologic toxicity Grade 4 neutropenia and thrombocytopenia	• Withhold treatment until recovery. Consider dose reduction for treatment resumption. A reduced dose must not be increased again. • If the same adverse drug reaction recurs at the reduced dose, discontinue treatment.

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

7.R.5.1 Dosage and administration of forodesine

The applicant's explanation about the proposed dosage and administration of forodesine:

In Study 116 conducted in healthy adults, $AUC_{0\text{-}24h}$ was higher in subjects receiving oral forodesine BID than in subjects receiving oral forodesine QD at the same dose [see Section "6.2.2.1 Foreign Phase I study"]. Increased C_{max} and $AUC_{0\text{-}24h}$ following oral forodesine BID were observed at the 300 mg dose as compared with the 200 mg dose. In contrast, the C_{max} and $AUC_{0\text{-}24h}$ following the 300 mg and 400 mg doses were similar [see Section "6.2.2.1 Foreign Phase I study"].

The Phase I of Study J02 was conducted based primarily on the study results above, and DLT was not observed at the 300 mg oral BID. The recommended dose of forodesine was thus determined to be 300 mg oral BID. In the Phase II of Study J02, oral forodesine was administered at 300 mg BID, and the clinical benefit of forodesine was demonstrated in patients with relapsed or refractory PTCL [see Section "7.R.2.1 Efficacy endpoints and results of efficacy evaluation"]. Therefore, the dosing regimen used in Study J02 was proposed for the dosage and administration for the application for marketing approval.

PMDA accepted the applicant's explanation.

7.R.5.2 Dose modifications for patients with renal impairment

The applicant's explanation about the dose modification of forodesine for patients with renal impairment:

In a foreign Phase I study (Study 112) in patients with renal impairment, the AUC_{last} following a single oral dose of forodesine 100 mg in patients with mild, moderate, and severe renal impairment was approximately 1.3, 1.5, and 1.8-fold, respectively, that of healthy adults with normal renal function [see Section "6.2.2.2 Foreign Phase I study in patients with renal impairment"].

In Study J02, CrCL of ≥50 mL/min was one of the inclusion criteria, and 18 subjects with normal renal function and 30 subjects with mild renal impairment were enrolled.

Table 18 summarizes safety data by severity of renal impairment in Studies 112 and J02.

Table 18. Summary of safety data by the severity of renal impairment (Studies 112 and J02)

	Number of subjects (%)					
	112				J02	
	Normal 9	Mild 8	Moderate 3	Severe 5	Normal 18	Mild 30
All adverse events	3 (33.3)	3 (37.5)	1 (33.3)	2 (40.0)	18 (100)	30 (100)
Grade ≥3 adverse events	0	0	0	0	17 (94.4)	29 (96.7)
Serious adverse events	0	0	0	0	4 (22.2)	15 (50.0)
Adverse events leading to treatment discontinuation	0	0	0	0	2 (11.1)	5 (16.7)
Adverse events leading to treatment interruption	0	0	0	0	5 (27.8)	9 (30.0)
Adverse events leading to dose reduction	0	0	0	0	1 (5.6)	0

In Study J02, the occurrence of adverse events was similar between subjects with normal renal function and those with mild renal impairment, and adverse events in subjects with mild renal impairment were able to be managed by dose interruption. Patients with moderate or severe renal impairment were excluded from Study J02, and therefore, the efficacy and safety of oral forodesine at 300 mg BID are not known in this patient population. For this reason, forodesine should be administered carefully to patients with moderate or severe renal impairment. In patients with severe renal impairment, AUC_{last} increased approximately 1.8-fold that of healthy adults [see Section "6.2.2.2 Foreign Phase I study in patients with renal impairment"], and, therefore, dose reduction to 200 mg should be considered.

Based on the above, the "Precautions for dosage and administration" section gives advice to the effect that:

- Due to the known increase in blood forodesine concentration in patients with moderate or severe renal impairment, their condition should be particularly carefully monitored for a sign of an adverse event during treatment. Particularly for patients with severe renal impairment, the dose may be reduced to 200 mg depending on the patient's condition.

PMDA's view:

In the main, the applicant's explanation is acceptable. However, there are no clinical study data on the efficacy and safety of oral forodesine300 mg BID in patients with moderate or severe renal impairment and oral forodesine 200 mg BID in patients with severe renal impairment. At present, this precludes a conclusion on a specific dosing regimen after dose reduction in these patients.

Accordingly, the "Precautions for dosage and administration" section should give the following cautionary advice. The efficacy and safety results from Study J02 by severity of renal impairment should be provided to healthcare professionals through written materials in an appropriate manner.

- Patients with renal impairment are known to have high blood forodesine concentration. Patients in this population may be treated with a reduced dose, and their condition should be particularly carefully monitored for a sign of an adverse event.

7.R.5.3 Dose modification of forodesine

PMDA asked the applicant to explain the dose modification of forodesine when adverse reactions occur.

The applicant's explanation:

In the Phase II of Study J02, the following dose modification criteria of forodesine including dose interruption were specified and the clinical benefit of forodesine was demonstrated by following the criteria. Therefore, the "Precautions for dosage and administration" section notes the importance of dose modification based on the criteria.

(a) Withhold forodesine if any of the following adverse drug reactions occurs following treatment. The patient should be treated appropriately depending on their condition. Dose interruption should be allowed for up to 2 weeks. Discontinue forodesine if the patient does not recover well enough to resume treatment.
    - Grade 3 or 4 non-hematologic toxicity (excluding untreated nausea, vomiting, and diarrhoea)
    - Neutrophil count decreased to $<500/mm^3$ lasting for ≥ 7 days
    - Platelet count decreased to $<25{,}000/mm^3$ lasting for ≥ 7 days (including cases of platelet transfusion)

(b) Resume forodesine at 200 mg BID after recovery from an adverse drug reaction in (a). No subsequent dose increase is allowed.

(c) Discontinue forodesine if any adverse drug reaction in (a) occurs during treatment at 200 mg BID.

(d) Withhold forodesine when necessary for the treatment of an adverse drug reaction other than mentioned in (a), with due observation of the patient's condition.

PMDA asked the applicant to explain dose modification of forodesine implemented in Study J02.

The applicant's explanation:

A total of 16 subjects experienced dose interruption according to the criteria given above (6 met Criterion [a] and 13 met Criterion [d], some subjects had >1 event). All events leading to dose interruption meeting Criterion (a) were of non-hematologic toxicity. In contrast, events leading to dose interruption meeting Criterion (d) were Grade 2 or 3 non-hematologic toxicity-related events or Grade 4 neutropenia or thrombocytopenia, except Grade 1 abdominal discomfort in 1 subject and dose interruption for an examination in 2 subjects. In 2 subjects experiencing Grade 4 neutropenia or thrombocytopenia, forodesine was suspended at the physician's discretion before the events had persisted for 7 days. Of those who underwent dose interruption according to Criteria (a) and (d), 1 and 8 subjects, respectively, recovered from the events and resumed the treatment. In Study J02, subjects experiencing dose interruption were to resume the treatment at a reduced dose of 200 mg. However, only 1 subject followed the rule about treatment resumption at the reduced dose. Therefore, sufficient clinical study data on the efficacy and safety of forodesine at the reduced dose of 200 mg BID are not available.

PMDA's view:

In the main, the applicant's explanation is acceptable. However, the "Precautions for dosage and administration" section should give the following cautionary advice in light of dose modification implemented in Study J02. Further, the dose modification criteria and a summary of patients who underwent dose interruption in Study J02 should be communicated to healthcare professionals using written materials in an appropriate manner.

- When forodesine causes any adverse drug reaction, corrective measures such as dose interruption may be taken according to the following criteria.

Criteria for dose interruption, dose reduction, and treatment discontinuation of forodesine

Adverse drug reaction*	Measures
Grade ≥3 non-hematologic toxicity Grade 4 neutropenia and thrombocytopenia	• Withhold treatment until recovery. Consider dose reduction for treatment resumption. A reduced dose must not be increased again. • If the same adverse reaction recurs at the reduced dose, discontinue treatment.

* Graded according to NCI-CTCAE v4.0

7.R.5.4 Co-administration with other antineoplastic drugs

The applicant explained that the efficacy and safety of forodesine co-administered with other antineoplastic drugs to patients with relapsed or refractory PTCL have not been established because of the current lack of clinical study results. This will be reminded in the "Precautions for dosage and administration" section.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

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

The applicant has a plan to conduct post-marketing surveillance covering all patients receiving forodesine to investigate the safety and other profiles of forodesine in post-marketing clinical use.

The key survey items of the post-marketing surveillance will be hematotoxicity, infections, and secondary malignancies, based on the incidences of adverse events in Studies J01 and J02.

The target sample size is 300 patients based on the incidences of adverse events, etc. in Study J02.

Hematotoxicity and infections, which are key survey items, occurred in many subjects within 52 weeks after the start of treatment in Study J02. For this reason, the observation period was determined to be 52 weeks, for being long enough to keep track of the occurrence of hematotoxicity and infections in post-marketing clinical use of forodesine. Secondary malignancies occurred ≥53 weeks after the start of treatment in Study J02. Therefore, patients are to be followed for 2 years from the start of treatment if continuing to receive forodesine Week 53 onward.

PMDA's view:

Due to the extremely limited safety data of forodesine in Japanese patients with relapsed or refractory PTCL, post-marketing surveillance should be conducted covering all patients receiving forodesine for a specified period in its post-marketing phase so that safety data can be collected promptly and in an unbiased manner. Obtained safety findings should be communicated to healthcare professionals immediately.

Key survey items of the post-marketing surveillance should be hematotoxicity, infections, secondary malignancies, peripheral nerve disorder, skin disorder, and cardiac failure, because treatment with forodesine requires attention to these adverse events, according to their occurrence in the Japanese and foreign clinical studies. The planned sample size and the duration of the observation period should be reconsidered in light of the occurrence of the additional adverse events defined as key survey items.

7.R.7 Development of forodesine for pediatric use

PMDA asked the applicant to explain the status of development of forodesine for children with relapsed or refractory PTCL. The applicant explained that currently there is no plan for development of forodesine for children with relapsed or refractory PTCL in Japan or other countries.

PMDA's view:
The applicant should gather and analyze information to explore the demand for forodesine for children. Depending on the outcome, a clinical study may be conducted in Japan, if necessary, or any other actions may be taken so that the development of forodesine for children with relapsed or refractory PTCL can be facilitated in an appropriate manner.

7.3 Adverse events in clinical studies

The following subsections describe major adverse events included in the clinical study data submitted for safety evaluation, except the results for death, which are described in Sections "7.1 Evaluation data" and "7.2 Reference data."

7.3.1 Japanese Phase I study (Study J01)

Adverse events occurred in 5 of 5 subjects (100%) in the 100 mg group, 3 of 3 subjects (100%) in the 200 mg group, and 5 of 5 subjects (100%) in the 300 mg group, and a causal relationship to the study drug could not be ruled out for events in any of these subjects. Table 19 lists adverse events that occurred in ≥2 subjects in any of the groups.

Table 19. Adverse events that occurred in ≥2 subjects in any groups

SOC PT (MedDRA/J ver.12.0)	Number of subjects (%)					
	100 mg 5		200 mg 3		300 mg 5	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events total	5 (100)	4 (80.0)	3 (100)	2 (66.7)	5 (100)	4 (80.0)
Blood and lymphatic system disorders						
Lymphopenia	0	0	2 (66.7)	2 (66.7)	2 (40.0)	2 (40.0)
Anaemia	1 (20.0)	0	1 (33.3)	0	2 (40.0)	1 (20.0)
Gastrointestinal disorders						
Constipation	3 (60.0)	0	1 (33.3)	0	2 (40.0)	0
Nausea	2 (40.0)	0	1 (33.3)	0	1 (20.0)	0
Skin and subcutaneous tissue disorders						
Erythema	2 (15.4)	0	0	0	0	0
Rash	1 (20.0)	0	2 (66.7)	0	2 (40.0)	0
General disorders and administration site conditions						
Oedema peripheral	0	0	2 (66.7)	0	1 (20.0)	0
Investigations						
Lymphocyte count decreased	4 (80.0)	3 (60.0)	1 (33.3)	0	3 (60.0)	2 (40.0)
Blood lactate dehydrogenase increased	2 (40.0)	0	1 (33.3)	0	2 (40.0)	0
Haemoglobin decreased	2 (40.0)	1 (20.0)	0	0	0	0
Neutrophil count decreased	0	0	2 (66.7)	0	1 (20.0)	0
White blood cell count decreased	0	0	1 (33.3)	0	2 (40.0)	0

Serious adverse events occurred in 2 of 5 subjects (40.0%) in the 100 mg, 1 of 3 subjects (33.3%) in the 200 mg group, and 1 of 5 subjects (20.0%) in the 300 mg group. The serious events were diverticulitis, large intestine carcinoma, DLBCL, herpes zoster, and viral infection (1 subject each, 7.7%) in the 100 mg group; cellulitis (1, 33.3%) in the 200 mg group; and herpes zoster (1, 20.0%) in the 300 mg group. A causal relationship to the study drug could not be ruled out for large intestine carcinoma, DLBCL, herpes zoster, and viral infection (1 each) in the 100 mg group; cellulitis (1) in the 200 mg group; and herpes zoster (1) in the 300 mg group.

Adverse events led to treatment discontinuation in 2 of 5 subjects (40.0%) in the 100 mg group. They were, namely, viral infection and DLBCL (1 each, 20.0%), and a causal relationship to the study drug could not be ruled out for either events.

7.3.2 Japanese Phase I/II study (Study J02)

Adverse events occurred in 48 of 48 subjects (100%), and a causal relationship to the study drug could not be ruled out for events in all these subjects. Table 20 lists adverse events with an incidence of ≥20%.

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

SOC PT (MedDRA/J ver.18.1)	Number of subjects (%) 48	
	All Grades	Grade ≥3
All adverse events	48 (100)	46 (95.8)
Infections and infestations		
Nasopharyngitis	12 (25.0)	0
Blood and lymphatic system disorders		
Anaemia	20 (41.7)	10 (20.8)
Metabolism and nutrition disorders		
Hypoalbuminaemia	12 (25.0)	2 (4.2)
Psychiatric disorders		
Insomnia	10 (20.8)	0
Nervous system disorders		
Headache	11 (22.9)	0
Gastrointestinal disorders		
Constipation	12 (25.0)	1 (2.1)
General disorders and administration site conditions		
Pyrexia	10 (20.8)	1 (2.1)
Investigations		
Lymphocyte count decreased	48 (100)	46 (95.8)
White blood cell count decreased	35 (72.9)	20 (41.7)
Neutrophil count decreased	26 (54.2)	16 (33.3)
Platelet count decreased	22 (45.8)	12 (25.0)
ALT increased	10 (20.8)	1 (2.1)

Serious adverse events occurred in 19 of 48 subjects (39.6%). They were, namely, pneumonia (4 subjects, 8.3%), pyrexia (3, 6.3%), bronchitis, gastroenteritis, gastrointestinal infection, upper respiratory tract infection, sinusitis fungal, pneumonia bacterial, pneumocystis jirovecii pneumonia, herpes zoster meningitis, acute myeloid leukaemia, DLBCL, EBV-associated lymphoma, anaemia, disseminated intravascular coagulation, histiocytosis haematophagic, hypersensitivity, hyperkalaemia, cerebral infarction, seizure, tonic convulsion, cataract nuclear, cardiac failure acute, dyspnoea, pleural effusion, ascites, ileus, small intestinal perforation, hepatic function abnormal, muscular weakness, malaise, and multi-organ failure (1 each, 2.1%). A causal relationship to the study drug could not be ruled out for pneumonia (4), bronchitis, gastroenteritis, gastrointestinal infection, upper respiratory tract infection, sinusitis fungal, pneumonia bacterial, pneumocystis jirovecii pneumonia, herpes zoster meningitis, DLBCL, EBV-associated lymphoma, anaemia, hypersensitivity, seizure, tonic convulsion, small intestinal perforation, muscular weakness, malaise, and pyrexia (1 each).

Adverse events to treatment discontinuation in 7 of 48 subjects (14.6%). These events were, namely, herpes zoster, pneumonia, acute myeloid leukaemia, EBV-associated lymphoma, histiocytosis haematophagic, peripheral sensory neuropathy, and muscular weakness (1 each, 2.1%). A causal relationship to the study drug could not be ruled out for herpes zoster, pneumonia, EBV-associated lymphoma, peripheral sensory neuropathy, and muscular weakness (1 each).

7.3.3 Foreign Phase I study (Study BCX1777-Hio 05-107)

Adverse events occurred in 13 of 15 subjects (86.7%) following oral administration in the fasted state, 15 of 18 subjects (83.3%) following oral administration after a meal, and 16 of 17 subjects (94.1%) following intravenous administration in the fasted state. A causal relationship to the study drug could

not be ruled out for events in 13 of 15 subjects (87%) following oral administration in the fasted state, 11 of 18 subjects (61.1%) following oral administration after a meal, and 16 of 17 subjects (94.1%) following intravenous administration in the fasted state. Table 21 lists adverse events that occurred in ≥2 subjects in any treatment period.

Table 21. Adverse events that occurred in ≥2 subjects in any treatment periods

SOC PT (MedDRA/J ver.12.0)	Number of subjects (%)					
	Oral administration in the fasted state 15		Oral administration after a meal 18		Intravenous administration in the fasted state 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	13 (86.7)	0	15 (83.3)	0	16 (94.1)	2 (11.8)
Nervous system disorders						
Headache	13 (86.7)	0	10 (55.6)	0	14 (82.4)	1 (5.9)
Dizziness	1 (6.7)	0	0	0	4 (23.5)	0
Respiratory, thoracic and mediastinal disorders						
Pharyngolaryngeal pain	0	0	2 (11.1)	0	1 (5.9)	0
General disorders and administration site conditions						
Chills	0	0	2 (11.1)	0	1 (5.9)	1 (5.9)
Gastrointestinal disorders						
Nausea	2 (13.3)	0	2 (11.1)	0	3 (17.6)	1 (5.9)
Vomiting	2 (13.3)	0	2 (11.1)	0	1 (5.9)	1 (5.9)
Infections and infestations						
Upper respiratory tract infection	0	0	2 (11.1)	0	1 (5.9)	0

There were no serious adverse events or adverse events leading to treatment discontinuation.

7.3.4 Foreign Phase I study (Study BCX1777-111)

Adverse events occurred in 28 of 35 subjects (80.0%) in the treatment period with the clinical study formulation, and 31 of 34 subjects (91.2%) in the treatment period with the commercial formulation. A causal relationship to the study drug could not be ruled out for events in 27 of 35 subjects (77.1%) in the treatment period with the clinical study formulation, and 30 of 34 subjects (88.2%) in the treatment period with the commercial formulation. Adverse events with an incidence of ≥20% in each treatment period were heart rate increased (15 of 35 subjects, 42.9%) and headache (14 of 35, 40.0%) in the treatment period with the clinical study formulation; and heart rate increased (21 of 34, 61.8%) and headache (16 of 34, 47.1%) in the treatment period with the commercial formulation

There were no serious adverse events or adverse events leading to treatment discontinuation.

7.3.5 Foreign Phase I study (Study BCX1777-112)

Adverse events occurred in 3 of 9 subjects (33.3%) in the group of patients with normal renal function, and 3 of 8 subjects (37.5%) in the group of patients with mild renal impairment, 1 of 3 subjects (33.3%) in the group of patients with moderate renal impairment, and 3 of 5 subjects (60.0%) in the group of patients with severe renal impairment. A causal relationship to the study drug could not be ruled out for events in 1 of 9 subjects (11.1%) in the normal renal function group and 2 of 8 subjects (25.0%) in the

mild renal impairment group. Adverse events that occurred in ≥2 subjects were nausea (2 subjects [8.0%] in the normal renal function group) and oedema peripheral (2 subjects [8.0%]; 1 each in the mild and severe renal function groups).

There were no serious adverse events or adverse events leading to treatment discontinuation.

7.3.6 Foreign Phase I study (Study BCX1777-116)

Adverse events occurred in 11 of 18 subjects (61.1%) in the 200 mg BID group, 13 of 16 subjects (81.3%) in the 300 mg BID group, 11 of 17 subjects (64.7%) in the 400 mg BID group, 8 of 15 subjects (53.3%) in the 400 mg QD group, 11 of 17 subjects (64.7%) in the 600 mg QD group, 11 of 18 subjects (61.1%) in the 800 mg QD group, and 38 of 47 subjects (80.9%) in the intravenous treatment group. A causal relationship to the study drug could not be ruled out for those in 9 of 18 subjects (50.0%) in the 200 mg BID group, 13 of 16 subjects (81.3%) in the 300 mg BID group, 11 of 17 subjects (64.7%) in the 400 mg BID group, 7 of 15 subjects (46.7%) in the 400 mg QD group, 11 of 17 subjects (64.7%) in the 600 mg QD group, 8 of 18 subjects (44.4%) in the 800 mg QD group, 32 of 47 subjects (68.1%) in the intravenous treatment group. Adverse events with an incidence of ≥20% were headache (7 of 18 subjects, 38.9%) and nausea (4 of 18, 22.2%) in the 200 mg BID group; headache (10 of 16, 62.5%), upper respiratory tract infection (4 of 16, 25.0%) and insomnia (4 of 16, 25.0%) in the 300 mg BID group; headache (11 of 17, 64.7%) in the 400 mg BID group; headache (4 of 15, 26.7%) in the 400 mg QD group; headache (9 of 17, 52.9%) in the 600 mg QD group; headache (6 of 18, 33.3%) in the 800 mg QD group; and headache (24 of 47, 51.1%) in the intravenous treatment group.

There were no serious adverse events.

Adverse events led to treatment discontinuation in 1 of 18 subjects (5.6%, chills) in the 200 mg BID group, 1 of 16 subjects (6.3%, influenza) in the 300 mg BID group, and 1 of 17 subjects (5.9%, upper respiratory tract infection) in the 600 mg QD group. A causal relationship to the study drug could not be ruled out for any of these event.

7.3.7 Foreign Phase I/II study (Study BCX1777-105)

Adverse events occurred in 3 of 3 subjects (100%) in the 40 mg/m^2 group, 34 of 34 subjects (100%) in the 80 mg/m^2 group, 3 of 3 subjects (100%) in the 160 mg/m^2 group, 14 of 15 subjects (93.3%) in the 300 mg/m^2 continuous treatment group, 4 of 5 subjects (80.0%) in the 300 mg/m^2 intermittent treatment group, and 4 of 4 subjects (100%) in the 320 mg/m^2 group. A causal relationship to the study drug could not be ruled out in 3 of 3 subjects (100%) in the 40 mg/m^2 group, 32 of 34 subjects (94.1%) in the 80 mg/m^2 group, 2 of 3 subjects (66.7%) in the 160 mg/m^2 group, 11 of 15 subjects (73.3%) in the 300 mg/m^2 continuous treatment group, 4 of 5 subjects (80.0%) in the 300 mg/m^2 intermittent treatment group, and 4 of 4 subjects (100%) in the 320 mg/m^2 group. Table 22 lists the adverse events with an incidence of ≥40% in any groups.

Table 22. Adverse events with an incidence of ≥40% in any groups

SOC PT (MedDRA/J ver.12.0)	Number of subjects (%)					
	40 mg/m^2 3		80 mg/m^2 34		160 mg/m^2 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	2 (66.7)	34 (100)	18 (52.9)	3 (100)	0
General disorders and administration site conditions						
Fatigue	3 (100)	0	16 (47.1)	0	0	0
Disease progression	2 (66.7)	0	9 (26.5)	2 (5.9)	0	0
Pyrexia	2 (66.7)	0	7 (20.6)	0	1 (33.3)	0
Oedema peripheral	0	0	13 (38.2)	0	2 (66.7)	0
Gastrointestinal disorders						
Nausea	2 (66.7)	0	14 (41.2)	0	2 (66.7)	0
Infections and infestations						
Impetigo	0	0	0	0	0	0
Pseudomonas infection	0	0	0	0	0	0
Sepsis	0	0	0	0	0	0
Nervous system disorders						
Dizziness	1 (33.3)	0	6 (17.6)	0	0	0
Skin and subcutaneous tissue disorders						
Swelling face	0	0	0	0	0	0
Skin fissures	0	0	0	0	0	0
Investigations						
Liver function test abnormal	0	0	1 (2.9)	0	0	0
Haemoglobin decreased	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	0	0	4 (11.8)	0	0	0
Psychiatric disorders						
Insomnia	0	0	6 (17.6)	0	2 (66.7)	0

Table 22. Adverse events with an incidence of ≥40% in any groups (cont.)

SOC PT (MedDRA/J ver.12.0)	Number of subjects (%)					
	300 mg/m^2 (continuous) 15		300 mg/m^2 (intermittent) 5		320 mg/m^2 4	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	14 (93.3)	7 (46.7)	4 (80.0)	3 (60.0)	4 (100)	2 (50.0)
General disorders and administration site conditions						
Fatigue	5 (33.3)	0	2 (40.0)	0	1 (25.0)	0
Disease progression	5 (33.3)	3 (20.0)	0	0	2 (50.0)	0
Pyrexia	4 (26.7)	0	1 (20.0)	0	1 (25.0)	0
Oedema peripheral	7 (46.7)	2 (13.3)	2 (40.0)	0	2 (50.0)	0
Gastrointestinal disorders						
Nausea	5 (33.3)	0	0	0	1 (25.0)	0
Infections and infestations						
Impetigo	0	0	0	0	2 (50.0)	0
Pseudomonas infection	3 (20.0)	0	2 (40.0)	0	0	0
Sepsis	2 (13.3)	0	2 (40.0)	0	0	0
Nervous system disorders						
Dizziness	0	0	0	0	2 (50.0)	0
Skin and subcutaneous tissue disorders						
Swelling face	0	0	0	0	2 (50.0)	1 (25.0)
Skin fissures	1 (6.7)	0	2 (40.0)	0	0	0
Investigations						
Liver function test abnormal	0	0	2 (40.0)	1 (20.0)	0	0
Haemoglobin decreased	1 (6.7)	0	2 (40.0)	1 (20.0)	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	1 (6.7)	0	2 (40.0)	0	1 (25.0)	0
Psychiatric disorders						
Insomnia	1 (6.7)	0	1 (20.0)	0	0	0

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 40 mg/m^2 group, 11 of 34 subjects (32.4%) in the 80 mg/m^2 group, 1 of 3 subjects (33.3%) in the 160 mg/m^2 group, 9 of 15 subjects (60.0%) in the 300 mg/m^2 continuous treatment group, 3 of 5 subjects (60.0%) in the 300 mg/m^2 intermittent treatment group, 1 of 4 subjects (25.0%) in the 320 mg/m^2 group. Serious adverse events occurring in ≥2 subjects were disease progression (4 subjects [6.3%]; 1 in the 80 mg/m^2 group and 3 in the 300 mg/m^2 continuous treatment group), sepsis (4 subjects [6.3%]; 3 in the 300 mg/m^2 continuous treatment group and 1 in the 300 mg/m^2 intermittent treatment group), pyrexia (2 subjects [3.1%]; 1 each in the 300 mg/m^2 continuous treatment group and in the 320 mg/m^2 group), cellulitis (2 subjects [3.1%]; 1 each in the 80 mg/m^2 group and in the 300 mg/m^2 continuous treatment group), and pneumonia (2 subjects [3.1%]; 1 each in the 80 mg/m^2 group and in the 300 mg/m^2 continuous treatment group). A causal relationship to the study drug could not be ruled out for pneumonia in 1 subject in the 80 mg/m^2 group, disease progression, sepsis, pyrexia, and pneumonia 1 subject each in the 300 mg/m^2 continuous treatment group.

Adverse events led to treatment discontinuation in 2 of 3 subjects (66.7%) in the 40 mg/m^2 group, 16 of 34 subjects (47.1%) in the 80 mg/m^2 group, 7 of 15 subjects (46.7%) in the 300 mg/m^2 continuous treatment group, 2 of 5 subjects (40.0%) in the 300 mg/m^2 intermittent treatment group, and 4 of 4 subjects (100%) in the 320 mg/m^2 group. Adverse events leading to treatment discontinuation occurred

in ≥2 subjects were disease progression (15 subjects [23.4%]; 1 in the 40 mg/m^2 group, 8 in the 80 mg/m^2 group, 4 in the 300 mg/m^2 continuous treatment group, 2 in the 320 mg/m^2 group), atrial fibrillation (2 subjects [3.1%]; 1 each in the 80 mg/m^2 group and in the 320 mg/m^2 group), pneumonia (2 subjects [3.1%]; 1 each in the 80 mg/m^2 group and in the 300 mg/m^2 continuous treatment group), liver function test abnormal (2 subjects [3.1%]; 1 each in the 80 mg/m^2 group and in the 300 mg/m^2 intermittent treatment group), and renal failure acute (2 subjects [3.1%]; 1 each in the 80 mg/m^2 group and in the 300 mg/m^2 continuous treatment group). A causal relationship to the study drug could not be ruled out for disease progression (5 subjects; 3 in the 80 mg/m^2 group, 1 in the 300 mg/m^2 continuous treatment group and 1 in the 320 mg/m^2 group), and liver function test abnormal (1 subject in the 300 mg/m^2 intermittent treatment group).

7.3.8 Foreign Phase II study (Study BCX1777-203)

Adverse events occurred in 138 of 144 subjects (95.8%), and a causal relationship to the study drug that could not be ruled out for events in 112 of 144 subjects (77.8%). The adverse event with an incidence of ≥20% was oedema peripheral (32 in 144 [22.2%]).

Serious adverse events occurred in 48 of 144 subjects (33.3%). Serious adverse events occurring in ≥2 subjects were mycosis fungoides (9 subjects, 6.3%), herpes zoster and skin infection (4 each, 2.8%), thrombocytopenia and septic shock (3 each, 2.1%), anaemia, atrial fibrillation, oedema peripheral, erysipelas, sepsis, and pruritus (2 each, 1.4%). A causal relationship to the study drug could not be ruled out for herpes zoster (3), anaemia, thrombocytopenia, sepsis, and skin infection (2 each), atrial fibrillation, oedema peripheral, erysipelas, and pruritus (1 each).

Adverse events led to treatment discontinuation or dose interruption of the study drug[22)] in 36 of 144 subjects (25.0%). Those occurring in ≥ 2 subjects were mycosis fungoides (8 subjects, 5.6%), herpes zoster (4, 2.8%), pruritus, sepsis, and thrombocytopenia (2 each, 1.4%). A causal relationship to the study drug could not be ruled out for herpes zoster (4), sepsis and thrombocytopenia (2 each), and pruritus (1).

7.3.9 Foreign Phase II study (Study BCX1777-204)

Adverse events occurred in 8 of 8 subjects (100%), and a causal relationship to the study drug could not be ruled out for events in 7 of 8 subjects (87.5%). Table 23 lists the adverse events with an incidence of ≥20%.

22) In this study, data of subjects experiencing treatment discontinuation and dose interruption were combined.

Table 23 Adverse events with an incidence of ≥20%

SOC PT (MedDRA/J ver.10.0)	Number of subjects (%) 8	
	All Grades	Grade ≥3
All adverse events	8 (100)	6 (75.0)
General disorders and administration site conditions		
Pyrexia	5 (62.5)	1 (12.5)
Blood and lymphatic system disorders		
Anaemia	2 (25.0)	2 (25.0)
Febrile neutropenia	2 (25.0)	2 (25.0)
Neutropenia	2 (25.0)	2 (25.0)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	3 (37.5)	1 (12.5)
Cough	3 (37.5)	0
Epistaxis	2 (25.0)	0
Gastrointestinal disorders		
Diarrhoea	2 (25.0)	0
Metabolism and nutritional disorders		
Hypomagnesaemia	2 (25.0)	0
Psychiatric disorders		
Insomnia	2 (25.0)	0
Skin and subcutaneous tissue disorders		
Night sweats	3 (37.5)	0

Serious adverse events occurred in 6 of 8 subjects (75.0%). These events were febrile neutropenia (2 subjects, 25.0%), abdominal pain, pyrexia, atrial fibrillation, infection, anaemia, cardiopulmonary failure, dyspnoea, hyperkalaemia, pneumonia, and pneumonitis (1 each, 12.5%). A causal relationship to the study drug could not be ruled out for pyrexia, atrial fibrillation, and febrile neutropenia (1 each).

There were no adverse events leading to treatment discontinuation.

7.3.10 Foreign Phase II study (Study BCX1777-210)

Adverse events occurred in 33 of 33 subjects (100%), and a causal relationship to the study drug could not be ruled out for events in 28 of 33 subjects (85%). Table 24 lists adverse events with an incidence of ≥20%.

Table 24. Adverse events with an incidence of ≥20%

SOC PT (MedDRA/J ver.10.1)	Number of subjects (%) 33	
	All Grades	Grade ≥3
All adverse events	33 (100)	18 (84.8)
General disorders and administration site conditions		
Fatigue	24 (72.7)	5 (15.2)
Oedema peripheral	15 (45.5)	0
Pyrexia	12 (36.4)	0
Gastrointestinal disorders		
Nausea	17 (51.5)	1 (3.0)
Diarrhoea	9 (27.3)	0
Blood and lymphatic system disorders		
Anaemia	14 (42.4)	8 (24.2)
Neutropenia	12 (36.4)	9 (27.3)
Febrile neutropenia	9 (27.3)	9 (27.3)
Thrombocytopenia	7 (21.2)	5 (15.2)
Infections and infestations		
Upper respiratory tract infection	10 (30.3)	2 (6.1)
Pneumonia	9 (27.3)	6 (18.2)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	12 (36.4)	1 (3.0)
Cough	10 (30.3)	0
Nervous system disorders		
Headache	13 (39.4)	0
Investigations		
Weight decreased	9 (27.3)	1 (3.0)
Skin and subcutaneous tissue disorders		
Rash	10 (30.3)	1 (3.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	7 (21.2)	0
Psychiatric disorders		
Insomnia	9 (27.3)	0

Serious adverse events occurred in 21 of 33 subjects (63.6%). These events were, namely, febrile neutropenia (8 subjects, 24.2%), pneumonia (6, 18.2%), cardiac failure congestive (3, 9.1%), pyrexia (2, 6.1%), nausea, medical observation, diarrhoea, primary hypogonadism, respiratory failure, bronchiolitis, autoimmune thrombocytopenia, ventricular tachycardia, pneumonia fungal, dehydration, haemorrhage intracranial, cerebrovascular accident, herpes zoster disseminated, septic shock, squamous cell carcinoma of skin, and chronic lymphocytic leukaemia (1 each, 3.0%). A causal relationship to the study drug could not be ruled out for febrile neutropenia (6), pneumonia (5), pyrexia (2), cardiac failure congestive, nausea, medical observation, primary hypogonadism, bronchiolitis, pneumonia fungal, cerebrovascular accident, herpes zoster disseminated, and squamous cell carcinoma of skin (1 each).

Adverse events led to treatment discontinuation in 7 of 33 subjects (21.2%). These events were, namely, fatigue (2 subjects, 6.1%); autoimmune thrombocytopenia, febrile neutropenia, malaise, weight decreased, white blood cell count increased, dizziness postural, haemorrhage intracranial, nausea, vomiting, pneumonia fungal, depression, pelvic discomfort, and cough (1 each, 3.0%). A causal relationship to the study drug could not be ruled out for fatigue (2), autoimmune thrombocytopenia, febrile neutropenia, malaise, weight decreased, dizziness postural, nausea, vomiting, pneumonia fungal, depression, pelvic discomfort, and cough (1 each).

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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.

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

The new drug application data (CTD 5.3.3.2.1, and CTD 5.3.5.2.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the whole, the clinical trial was implemented in accordance with GCP; therefore, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the inspection revealed the following issues at some study centers, albeit with no major impact on the overall study evaluation. These issues were notified to the heads of the study centers as areas for improvement.

Areas for improvement

Study centers

- A protocol deviation (non-compliance with the specifications about the dose level of the study drug after dose interruption)
- A failure to provide information to some subjects that may have influenced their willingness to continue participation in the clinical study.
- A missing record of the provision of information to some subjects at blood recollection and their consent to the continued participation in a clinical study.

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

PMDA has concluded that the data submitted demonstrate the efficacy of forodesine in the treatment of relapsed or refractory PTCL and acceptable safety in view of the benefits. Forodesine is a drug with a new active ingredient that inhibits PNP, an enzyme known to be necessary for T cell proliferation, increasing dGuo accumulation in the cell and inducing apoptosis, thereby inhibiting the proliferation of T cell-derived malignancies. Forodesine is clinically significant because it offers a new treatment option for patients with relapsed or refractory PTCL. The efficacy, indication, post-marketing issues, etc. should be further investigated.

PMDA has concluded that forodesine may be approved if forodesine is not considered to have any

particular problems based on comments from the Expert Discussion.

Review Report (2)

February 20, 2017

Product Submitted for Approval

Brand Name	Mundesine Capsule 100 mg
Non-proprietary Name	Forodesine Hydrochloride
Applicant	Mundipharma K.K.
Date of Application	June 7, 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

In view of the discussions presented in Section "7.R.2 Efficacy" of Review Report (1), PMDA concluded that the efficacy of forodesine in the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) has been demonstrated based on the results of Phase II of the Japanese Phase I/II study (Study FDS-J02, referred to as Study J02) in patients with relapsed or refractory PTCL, which indicated that the observed response met the criteria prespecified in the protocol.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

In view of the discussions presented in Section "7.R.3 Safety" of Review Report (1), PMDA concluded that the use of forodesine requires attention to adverse events, in particular, hematotoxicity, infections, secondary malignancies, peripheral nerve disorder, skin disorder, and cardiac failure.

PMDA concluded that forodesine is tolerated in patients when they are followed by a physician with adequate knowledge and experience in the treatment of hematopoietic malignancy by appropriate means including monitoring and control of adverse events, dose interruption or reduction, and treatment discontinuation.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion. Furthermore, the following issue was raised by the expert advisors:

- Angioimmunoblastic T-cell lymphoma, a type of PTCL, is known to be complicated by Epstein-

Barr virus (EBV)-associated lymphoproliferative disorders (EBV-LPD) or EBV-associated malignant lymphoma to some extent. However, the incidence of EBV-associated malignant lymphoma was significantly high in Study J02. Therefore, strategies for early diagnosis and appropriate measures should be discussed particularly for EBV-associated malignant lymphoma, which is one of secondary malignancies. At the same time, information on these adverse events should be provided to healthcare professionals in an appropriate manner.

PMDA asked the applicant to explain (a) the occurrence of EBV-LPD and EBV-associated malignant lymphoma in clinical studies of other antineoplastic drugs in patients with PTCL, and (b) the necessity of cautionary advice on EBV-LPD and EBV-associated malignant lymphoma caused by forodesine.

The applicant's explanation:
In clinical studies on other antineoplastic drugs in patients with PTCL (romidepsin [unapproved in Japan], belinostat [unapproved in Japan], pralatrexate [unapproved in Japan], brentuximab vedotin [genetical recombination], and mogamulizumab [genetical recombination]) (e.g., *Blood.* 2011;117:5827-34, *J Clin Oncol.* 2015;33:4292-9, *J Clin Oncol.* 2011;29:1182-9, *J Clin Oncol.* 2012;30:2190-6, *J Clin Oncol.* 2014;32:1157-64), EBV-LPD or EBV-associated malignant lymphoma were reported in the foreign Phase II clinical study of romidepsin (1 of 47 subjects, 2.1%). Based also on the action mechanism of forodesine, the risk for developing EBV-LPD or EBV-associated malignant lymphoma following the administration of forodesine may be high.

Early diagnosis is extremely important for EBV-LPD and EBV-associated malignant lymphoma. During treatment with forodesine, the patient's condition should be carefully monitored by diagnostic imaging, etc. such as CT on a regular basis. A lymph node biopsy should be performed as early as possible when EBV-LPD or EBV-associated malignant lymphoma is suspected, and it should be appropriately treated. This advice must be given to healthcare professionals through the package insert.

PMDA's view:
In light of the incidence of EBV-LPD and EBV-associated malignant lymphoma in clinical studies of other antineoplastic drugs in patients with PTCL, the incidence of EBV-LPD and EBV-associated malignant lymphoma in Study J02 (4 of 48 subjects, 8.3%), and the incidence of EBV-associated malignant lymphoma in Study J01 (1 of 13 subjects, 7.7%), despite different dosing regimen from that of Study J02, the risk or forodesine to cause EBV-LPD or EBV-associated malignant lymphomamay be high.

Accordingly, PMDA requested that the applicant gives cautionary advice on EBV-LPD and EBV-associated malignant lymphoma appropriately as discussed above, and the applicant agreed.

1.3 Clinical positioning and indication

In view of the discussions presented in Section "7.R.4 Clinical positioning and indication" in Review

Report (1), forodesine can be positioned as a treatment option for patients with relapsed or refractory PTCL; therefore, PMDA concluded that the indication of forodesine should be "relapsed or refractory peripheral T-cell lymphoma" as proposed by the applicant. The histopathological types eligible for Study J02 should be informed in the "Clinical studies" section of the package insert, with the following reminders in the "Precautions for indication" section.

Precautions for indication

- A disease to be treated with forodesine should be confirmed by physicians or at medical centers with adequate experience in pathological diagnosis.
- Treating physicians must determine if the patient is suitable for the use of forodesine based on a good knowledge from the "Clinical studies" section, such as the histopathological types of patients enrolled in clinical studies, and adequate understanding of the efficacy and safety of forodesine.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA requested that the applicant describe the "Indications" and "Precautions for indication" sections as discussed above, and the applicant agreed.

1.4 Dosage and administration

In view of the discussions presented in Section "7.R.5 Dosage and administration" in Review Report (1), PMDA concluded that the cautionary statements should be provided as shown below in the "Precautions for dosage and administration" section, and the dosage and administration for forodesine should be specified as follows: "The usual adult dosage is 300 mg of oral forodesine administered twice daily. The dose should be reduced according to the patient's condition."

Precautions for dosage and administration

- The efficacy and safety of forodesine used with other antineoplastic drugs have not been established.
- Patients with renal impairment are known to have high blood forodesine concentration. Patients in this population may be treated with a reduced dose, and their condition should be particularly carefully monitored for a sign of an adverse event.
- When forodesine causes any adverse drug reaction, corrective measures such as dose interruption may be taken according to the following criteria.

Criteria for dose interruption, dose reduction, and treatment discontinuation of forodesine

Adverse reaction*	Measures
Grade ≥3 non-hematologic toxicity Grade 4 neutropenia and thrombocytopenia	• Withhold treatment until recovery. Consider dose reduction for treatment resumption. A reduced dose must not be increased again. • If the same adverse drug reaction recurs at the reduced dose, discontinue treatment.

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

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA requested that the applicant describe the "Dosage and administration" and "Precautions for dosage and administration" section as shown above, and the applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance covering all patients receiving forodesine to investigate its safety in post-marketing clinical use. The target sample size is 300, and the planned observation period is 52 weeks after the start of treatment. The applicant also plans to conduct post-marketing surveillance on secondary malignancies for up to 2 years after the start of treatment in patients receiving forodesine for ≥52 weeks.

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" of Review Report (1), PMDA concluded that post-marketing surveillance covering all patients receiving forodesine for a specified time period after its market launch so that safety data are collected early and in unbiased manner. Obtained safety findings should be communicated to healthcare professionals promptly. The following are further surveillance-related decisions:

- The key survey items are hematotoxicity, infections, secondary malignancies, peripheral nerve disorder, skin disorder, and cardiac failure, which are potential adverse events of forodesine, based on the incidences of adverse events in the Japanese and foreign clinical studies.
- The planned sample size and the duration of the observation period should be reconsidered in light of the additional the key survey items based on the occurrence of these adverse events in Study J02.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion. Furthermore, the following issues were raised by the expert advisors:

- The incidence of EBV-associated malignant lymphoma in Study J02 was significantly high [see Section "1.2 Safety" of Review Report (2)]; therefore, the key survey items should also cover the event.

In response to the discussions at the Expert Discussion, PMDA requested that the applicant re-examine the post-marketing surveillance plan.

The applicant's response:

- Key survey items are hematotoxicity, infections, EBV-associated malignant lymphoma (including EBV-LPD), secondary malignancies other than EBV-associated malignant lymphoma, peripheral

nerve disorder, skin disorder, and cardiac failure.

- The planned sample size is 160 (143 patients to be included in the safety analysis set), based on the incidences of adverse events specified as key survey items in Study J02.
- The duration of the observation period will be 24 weeks after the start of forodesine treatment based on the occurrence of hematotoxicity, infections, peripheral nerve disorder, skin disorder, and cardiac failure in Study J02. The observation period of EBV-associated malignant lymphoma (including EBV-LPD), and secondary malignancies other than EBV-associated malignant lymphoma will be continued up to 2 years after the start of treatment, based on the occurrence of the event in Study J02.

PMDA accepted the applicant's explanation.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) should include the safety and efficacy specifications presented in Table 25, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 26.

Table 25. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hematotoxicity • Infections • EBV-associated malignant lymphoma (including EBV-LPD)	• Secondary malignancies other than EBV-associated malignant lymphoma • Peripheral nerve disorder • Skin disorder • Cardiac failure • Safety in patients with renal impairment	• Not specified
Efficacy specification		
• Efficacy in clinical use		

Table 26. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing surveillance (all case surveillance)	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate information (through information materials for healthcare professionals)

Table 27. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety of forodesine in its post-marketing clinical use
Survey method	All-case surveillance
Population	All patients treated with forodesine
Observation period	24 weeks after the start of treatment (2 years after the start of treatment for EBV-associated malignant lymphoma, including EBV-LPD, and secondary malignancies other than EBV-associated malignant lymphoma)
Planned sample size	160 patients
Main survey items	Patient characteristics (age, histopathological type, complications, medical history), prior treatment, forodesine treatment status, concomitant drugs, adverse events, efficacy (response rate), etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indication and dosage and administration, based on the conditions for approval as shown below. However, the applicant must ensure that the package insert gives necessary cautionary advice, information related to the proper use of forodesine is disseminated appropriately during the post-marketing phase, and the product is used properly under the supervision of a physician with adequate knowledge and experience in treating hematopoietic malignancy at a medical facility capable of emergency care. The product is an orphan drug with a re-examination period of 10 years. The product is not classified as a biological product or a specified biological product. The drug substance and the drug product are both classified as powerful drugs.

Indication

Relapsed or refractory peripheral T-cell lymphoma

Dosage and Administration

The usual adult dosage is 300 mg of oral forodesine administered twice daily. The dose should be reduced according to the patient's condition.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of patients participated in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data of a certain number of patients are accumulated to identify the characteristics of treated patients and to collect safety and efficacy data early. Based on the data obtained, the applicant should take necessary measures to ensure the proper use of the product.

Warning(s)

The product should be administered only when determined appropriate by a physician with adequate knowledge and experience in treating hematopoietic malignancy at a medical facility capable of emergency care. Treatment with the product should be started only after obtaining consent to thorough explanation about the product's efficacy and risks given to the patient or their family member.

Contraindication(s)

Patients with a history of hypersensitivity to any ingredients of the product

Precautions for Indication(s)

1. A disease to be treated with the product should be confirmed by physicians or at medical centers with adequate experience in pathological diagnosis.
2. Treating physicians must determine if the patient is suitable for the use of forodesine based on a good knowledge from the "Clinical studies" section, such as the histopathological types of patients

enrolled in the clinical studies, and adequate understanding of the efficacy and safety of the product.

Precautions for Dosage and Administration

1. The efficacy and safety of the product used with other antineoplastic drugs have not been established.
2. Patients with renal impairment are known to have high blood forodesine concentration. Patients in this population may be treated with a reduced dose, and their condition should be particularly carefully monitored for a sign of an adverse event.
3. When forodesine causes any adverse drug reaction, corrective measures such as dose interruption may be taken according to the following criteria.

Criteria for dose interruption, dose reduction, and treatment discontinuation of the product

Adverse drug reaction*	Measures
Grade ≥3 non-hematologic toxicity Grade 4 neutropenia and thrombocytopenia	• Withhold treatment until recovery. Consider dose reduction for treatment resumption. A reduced dose must not be increased again. • If the same adverse drug reaction recurs at the reduced dose, discontinue treatment.

* Graded according to NCI-CTCAE v4.0