Report on the Deliberation Results

March 6, 2023

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Valixa Dry Syrup 5000 mg
Non-proprietary Name	Valganciclovir Hydrochloride (JAN*)
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	June 30, 2022

Results of Deliberation

In its meeting held on February 27, 2023, the Second Committee on New Drugs concluded that the application for partial change approval of the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

February 16, 2023
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	Valixa Dry Syrup 5000 mg
Non-proprietary Name	Valganciclovir Hydrochloride
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	June 30, 2022
Dosage Form/Strength	Dry syrup: Each bottle (12.0 g) contains 5.51 g of valganciclovir hydrochloride (5.00 g of valganciclovir).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 543 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 0526-14 dated May 26, 2022, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of symptomatic congenital cytomegalovirus disease, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indications

Cytomegalovirus disease in the following patients:

- Patients with acquired immunodeficiency syndrome
- Organ transplant recipients (including hematopoietic stem cell transplant recipients)

- Patients with malignant tumors

Prevention of cytomegalovirus disease in organ transplant recipients (excluding hematopoietic stem cell transplant recipients)

Symptomatic congenital cytomegalovirus disease

(Underline denotes additions.)

Dosage and Administration

Cytomegalovirus disease

Initial therapy

The usual adult dosage is 900 mg of valganciclovir administered orally twice daily after meals.

Maintenance therapy

The usual adult dosage is 900 mg of valganciclovir administered orally once daily after a meal.

Prevention of cytomegalovirus disease in organ transplant recipients (excluding hematopoietic stem cell transplant recipients)

The usual adult dosage is 900 mg of valganciclovir administered orally once daily after a meal.

The usual pediatric dosage is the dose determined according to the equation shown below, administered orally once daily after a meal. The daily dose should not exceed 900 mg. If the patient's estimated glomerular filtration rate (eGFR) is >150, the eGFR value in the equation should be 150.

Dose (mg) = 7 × body surface area (m^2) × eGFR (mL/min/1.73 m^2)

Symptomatic congenital cytomegalovirus disease

The usual dosage for neonates and infants is 16 mg/kg of valganciclovir administered orally twice daily.

(Underline denotes additions.)

Approval Condition

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

Attachment

Review Report (1)

February 1, 2023

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

Product Submitted for Approval

Brand Name	Valixa Dry Syrup 5000 mg
Non-proprietary Name	Valganciclovir Hydrochloride
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	June 30, 2022
Dosage Form/Strength	Dry syrup: Each bottle (12.0 g) contains 5.51 g of valganciclovir hydrochloride (5.00 g of valganciclovir).

Proposed Indications:

Cytomegalovirus disease in the following patients:

- Patients with acquired immunodeficiency syndrome
- Organ transplant recipients (including hematopoietic stem cell transplant recipients)
- Patients with malignant tumors

Prevention of cytomegalovirus disease in organ transplant recipients (excluding hematopoietic stem cell transplant recipients)

Treatment of symptomatic congenital cytomegalovirus disease

(Underline denotes additions.)

Proposed Dosage and Administration

Cytomegalovirus disease

Initial therapy

The usual adult dosage is 900 mg of valganciclovir administered orally twice daily after meals.

Maintenance therapy

The usual adult dosage is 900 mg of valganciclovir administered orally once daily after a meal.

Prevention of cytomegalovirus disease in organ transplant recipients (excluding hematopoietic stem cell transplant recipients)

The usual adult dosage is 900 mg of valganciclovir administered orally once daily after a meal.

The usual pediatric dosage is the dose determined according to the equation shown below, administered orally once daily after a meal. The daily dose should not exceed 900 mg. If the patient's estimated glomerular filtration rate (eGFR) is >150, the eGFR value in the equation should be 150.

Dose (mg) = 7 × body surface area (m^2) × eGFR (mL/min/1.73 m^2)

Treatment of symptomatic congenital cytomegalovirus disease

The usual dosage for neonates and infants is 16 mg/kg of valganciclovir administered orally twice daily.

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

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

Valganciclovir hydrochloride (hereinafter referred to as valganciclovir), which was developed by F. Hoffmann-La Roche (Switzerland), is a prodrug designed to increase the oral absorption of ganciclovir (GCV). Orally administered valganciclovir is hydrolyzed in the intestinal wall, liver, etc. for conversion into GCV. In cytomegalovirus (CMV)-infected cells, the GCV, after being phosphorylated by viral enzymes such as protein kinases, inhibits the replication of the viral genome via competitive inhibition of the uptake of deoxyguanosine triphosphate into deoxyribonucleic acid (DNA). Valganciclovir thus exerts its antiviral activity against herpes viruses such as CMV.

In Japan, Valixa Tablets 450 mg, a drug product containing valganciclovir as the active ingredient, was first approved in November 2004 for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome, and was subsequently approved for the treatment of CMV disease in patients with acquired immunodeficiency syndrome, organ transplant (including hematopoietic stem cell transplant) recipients, and patients with malignant tumors, and for the prevention of CMV disease in organ transplant recipients (excluding hematopoietic stem cell transplant recipients). In August 2018, when a pediatric dosage for the prevention of CMV disease in organ transplant recipients (excluding hematopoietic stem cell transplant recipients) was added, a new dosage form, Valixa Dry Syrup 5000 mg (the drug product reviewed in the present application) was approved. Valganciclovir has been approved for similar indications and used in clinical practice in 82 countries and regions including the US and Europe.

Congenital CMV disease occurs when the virus is transmitted from a mother to the fetus through the placenta after the mother has experienced an initial infection, reinfection, or reactivation of CMV during pregnancy. Roughly 30% to 40% of patients with congenital CMV disease are diagnosed with symptomatic congenital CMV disease, which causes symptoms such as microcephaly, hepatosplenomegaly, convulsive seizure, periventricular calcification, sensorineural hearing loss, and chorioretinopathy (*BMJ Open.* 2011;1:e000118, *J Infect Chemother.* 2020;26:790-4, etc.). Roughly 40% to 90% of patients with symptomatic congenital CMV disease have residual neurological sequelae including sensorineural hearing loss, mental retardation, and movement disorder (*Rev Med Virol.* 2007;17:355-63, *J Pediatr.* 2014;164:855-9).

In an investigator-initiated, randomized, comparative study of GCV, the active parent drug of valganciclovir, in patients with symptomatic congenital CMV disease (foreign Study CASG102), hearing deterioration was inhibited and mental retardation was improved in patients treated with intravenous GCV for 6 weeks, as compared with untreated patients (*J Pediatr.* 2003;143:16-25, *J Clin Virology.* 2009;46 Suppl 4:S22-6). Another investigator-initiated, randomized, comparative study (foreign Study CASG112) showed better developmental outcomes in patients receiving valganciclovir for 6 months than in those receiving the drug for 6 weeks (*N Engl J Med.* 2015;372:933-43). Based on these study reports and other findings, the treatment guidelines by the International Congenital Cytomegalovirus Recommendations Group and the European Society of Paediatric Infectious Diseases (*Lancet Infect Dis.* 2017;17:e177-88 and *Pediatr Infect Dis J.*

2017;36:1205-13) have recommended pharmacotherapy with valganciclovir for patients with moderate to severe symptomatic congenital CMV disease [Table 1].

Table 1. Definition of the severity of symptomatic congenital CMV disease and recommendation on the use of valganciclovir in foreign treatment guidelines

	International Congenital Cytomegalovirus Recommendations Group[a)]		European Society of Paediatric Infectious Diseases[b)]	
	Definition	Use of valganciclovir	Definition	Use of valganciclovir
Mild	•Presence of 1 or 2 primary disease-associated transient clinical manifestations (e.g., mild hepatomegaly, transient thrombocytopenia, or raised ALT)	Not recommended	•Presence of 1 or 2 primary disease-associated transient clinical manifestations (e.g., petechiae, mild hepatomegaly or splenomegaly, laboratory abnormalities [e.g., thrombocytopenia, anemia, leukopenia, and abnormal liver function test results], or small for gestational age (SGA) without microcephaly)	Not recommended
Moderate	•Presence of multiple primary disease-associated clinical manifestations (thrombocytopenia, petechiae, hepatomegaly, splenomegaly, fetal growth restriction, or hepatitis [raised transaminase or bilirubin]) •Central nervous system (CNS) involvement (microcephaly, abnormal brain imaging consistent with the primary disease, chorioretinopathy, sensorineural hearing loss, abnormal cerebrospinal fluid level, or CMV DNA in the cerebrospinal fluid)	Recommended[c)]	•Primary disease-associated persistent (≥2 weeks) laboratory abnormalities (e.g., thrombocytopenia and abnormal liver function test results), or ≥3 mild clinical manifestations (e.g., thrombocytopenia, petechiae, hepatosplenomegaly, and abnormal liver function test results)	Recommended[d)]
Severe			•CNS involvement (abnormal neurologic or ophthalmologic examination, microcephaly or abnormal neuroimaging consistent with the primary disease, or sensorineural hearing loss) •Life-threatening disease •Severe single-organ disease (clinically significant abnormal liver function test results, or marked hepatosplenomegaly) •Multiorgan involvement without CNS involvement	

a) *Lancet Infect Dis.* 2017;17:e177-88
b) *Pediatr Infect Dis J.* 2017;36:1205-13
c) The recommended duration of valganciclovir therapy is 6 months.
d) The recommended duration of valganciclovir therapy is 6 months in patients with CNS involvement or usually 6 months (≥6 weeks) in patients without CNS involvement.

Using the above-mentioned foreign clinical studies as a guide, an investigator-initiated study was conducted in Japanese patients with symptomatic congenital CMV disease (Japanese Study VGCV-1). The applicant concluded that Study VGCV-1 demonstrated the efficacy and safety of Valixa Dry Syrup in the treatment of symptomatic congenital CMV disease, and therefore has filed an application for partial change approval to add a new indication and a new dosage of valganciclovir.

As of March 2022, valganciclovir has not been approved for symptomatic congenital CMV disease in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no additional data on quality have been submitted.

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

Since the present application is intended for a new indication and a new dosage, no additional data on non-clinical pharmacology have been submitted.

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

Since the present application is intended for a new indication and a new dosage, no additional data on non-clinical pharmacokinetics have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no additional data on toxicity have been submitted.

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

A commercially available valganciclovir formulation was used in the Japanese clinical study (Study VGCV-1) conducted for the present application and a foreign clinical study (Study CASG112). Human plasma GCV concentrations were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS), with a lower limit of quantification of 0.04 μg/mL.

6.2 Clinical pharmacology

6.2.1 Japanese clinical study (CTD 5.3.5.2-1, Study VGCV-1, February 2020 to May 2021)

In Japanese patients with symptomatic congenital CMV disease who received oral valganciclovir 16 mg/kg twice daily, the plasma GCV concentration (mean ± standard deviation [SD]) at Week 6 (90 minutes after the last dose) was 4.59 ± 1.31 μg/mL (in 23 patients with evaluable pharmacokinetic [PK] data).

6.R Outline of the review conducted by PMDA

6.R.1 Dosage regimen for patients with symptomatic congenital CMV disease

The applicant explained that the dosage regimen of "valganciclovir 16 mg/kg orally twice daily for 6 months" was selected for Study VGCV-1 involving Japanese patients with symptomatic congenital CMV disease, based on (a) the findings mentioned below and (b) the dosage regimen of valganciclovir for symptomatic congenital CMV disease recommended by the foreign guidelines (*Lancet Infect Dis.* 2017;17:e177-88 and *Pediatr Infect Dis J.* 2017;36:1205-13).

- In Study CASG102 involving non-Japanese patients with symptomatic congenital CMV disease, GCV 6 mg/kg intravenously administered twice daily for 6 weeks inhibited the deterioration of hearing loss level [see Section 7.R.2.1].
- The dosage regimen used in Study CASG112 in non-Japanese patients with symptomatic congenital CMV disease was valganciclovir 16 mg/kg twice daily, because the dosage was expected to yield an exposure

to GCV (the active parent drug of valganciclovir) comparable to the plasma GCV exposure ($AUC_{0\text{-}12h}$, 27 mg·h/L)[1)] estimated in Study CASG102.[2)]

- Non-clinical study results have suggested that long-term valganciclovir therapy may pose carcinogenic risks, and no clinical study results are available regarding the safety of valganciclovir administered for >6 months.
- The dosage and administration of valganciclovir for the approved indications (pediatric solid organ transplant recipients and adult patients) is the same in Japan and other countries or areas (see Review Report for Valixa Tablets 450 mg, etc. dated July 23, 2018 [in Japanese]), and the selected dosage regimen was expected to yield GCV exposure comparable to that observed in pediatric solid organ transplant recipients, an approved indication.[3)]

The approved dosage and administration of valganciclovir recommends that it be taken after meals, based on food effect study results.[4)] However, no instructions regarding dosing timing in relation to meals were provided in Study VGCV-1, in view of (a) the frequency of meals (feeding or baby food) in neonates and infants (the intended population of valganciclovir therapy for the present application) and (b) the fact that the foreign treatment guidelines for symptomatic congenital CMV disease provide no recommendation on dosing timing in relation to meals.

PMDA accepted the applicant's rationale for the dosage regimen selected for Study VGCV-1.

6.R.2 Effects of renal function on the PK of valganciclovir

Since the major elimination route of GCV, the active metabolite of valganciclovir, is renal excretion, the applicant provided the following explanation about the effects of renal function on the PK of valganciclovir administered at the proposed dosage and administration:

The applicant's explanation:

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1) Although no PK evaluation was conducted in Study CASG102, the target plasma exposure to GCV was set based on the plasma GCV exposure (median $AUC_{0\text{-}12h}$, 27 mg·h/L) observed in a foreign study in which GCV was administered at the same dosage regimen (intravenous GCV 6 mg/kg twice daily) to patients with symptomatic congenital CMV disease (*Clin Pharmacol Ther.* 1993;53:15-21).

2) In a foreign study (Study CASG109), the PK following the administration of a GCV intravenous formulation or a valganciclovir oral formulation (the proposed product in the present application) was evaluated in non-Japanese patients with symptomatic congenial CMV disease. The results showed that the plasma GCV exposure following administration of oral valganciclovir at approximately 16 mg/kg twice daily (geometric mean $AUC_{0\text{-}12h}$, 27.35 mg·h/L) was comparable to the plasma GCV exposure following administration of intravenous GCV 6 mg/kg twice daily (median $AUC_{0\text{-}12h}$, 27 mg·h/L) (*J Infect Dis.* 2008:197; 836-45).

3) The plasma GCV exposure ($AUC_{0\text{-}24h}$) at a daily dose of valganciclovir did not differ largely between patients with symptomatic congenital CMV disease (54.7 mg·h/L[a)]) and pediatric solid organ transplant recipients, an approved indication (35.6-69.4 mg·h/L[b)]).
   a) A value that was twice the plasma GCV exposure ($AUC_{0\text{-}12h}$) following administration of oral valganciclovir at approximately 16 mg/kg twice daily (geometric mean, 27.35 mg·h/L; *J Infect Dis.* 2008:197;836-45) in patients with symptomatic congenital CMV disease
   b) A plasma GCV exposure (mean $AUC_{0\text{-}24h}$) following administration of oral valganciclovir at the approved dosage (the dose calculated by the following equation was orally administered once daily after a meal: Dose [mg] = 7 × body surface area [m^2] × estimated glomerular filtration rate [mL/min/1.73 m^2]) in pediatric kidney, liver, or heart recipients (*Am J Transplant.* 2009:9;636-43)

4) The plasma GCV exposure ($AUC_{0\text{-}24h}$) following administration of oral valganciclovir tablets 875 mg under fasted or fed conditions once daily for 3 days was monitored in HIV- and CMV-positive patients aged ≥18 years. The results showed that the $AUC_{0\text{-}24h}$ under fed conditions was approximately 30% higher than that under fasted conditions (*Clin Pharmacokinet.* 1999;37:167-76).

Table 2 shows the gestational age at birth, body weight, and plasma GCV concentrations at Week 6 (90 minutes after the last dose) in patients receiving oral valganciclovir 16 mg/kg twice daily, by renal function (CLcr [Schwartz formula][5)]) at baseline and Week 6, in Study VGCV-1.

Table 2. Gestational age at birth, body weight, and plasma GCV concentrations at Week 6 (90 minutes after the last dose) by renal function (CLcr) at baseline and Week 6 in Study VGCV-1

CLcr range (mL/min/1.73 m^2)	By CLcr at baseline				By CLcr at Week 6			
	n	Gestational age at birth (weeks)	Body weight (g)	GCV concentration at Week 6 (μg/mL)	n	Gestational age at birth (weeks)	Body weight (g)	GCV concentration at Week 6 (μg/mL)
<20	0	-	-	-	0	-	-	-
≥20 and <40	11	36.6 [34, 41]	2,607 [1,822, 3,536]	4.56±1.54 a) b)	0	-	-	-
≥40 and <60	8	37.9 [34, 41]	3,640 [2,665, 4,460]	4.49±1.27 c)	14	36.5 [34, 41]	4,404 [3,141, 5,500]	4.41±1.38 b) c)
≥60	5	38.6 [38, 40]	4,298 [3,556, 5,400]	4.82±1.08	9	39.0 [38, 41]	5,768 [4,815, 6,740]	4.86±1.20

Gestational age at birth and body weight, mean [range]; plasma GCV concentration, mean ± SD; -, not applicable
a) n = 10
b) Including 1 patient who experienced dose reduction (16 mg/kg once daily) due to an adverse event at the PK assessment point (Week 6) (plasma GCV concentration, 4.01 μg/mL), and 1 patient who experienced treatment interruption just before the PK assessment (3 days before the PK assessment day) due to an adverse event (plasma GCV concentration, 7.32 μg/mL)
c) Including 1 patient who experienced dose reduction (16 mg/kg once daily) due to an adverse event at the PK assessment point (Week 6) (plasma GCV concentration, 3.66 μg/mL)

The inter-patient differences in renal function (CLcr) at baseline or Week 6 observed in Study VGCV-1 are likely to reflect the development of renal function in individual subjects, given the gestational age at birth and body weight in the subpopulations by renal function (CLcr) [Table 2]. However, the plasma GCV concentration at Week 6 did not differ largely between the subpopulations. Therefore, it is unnecessary to adjust the dose of valganciclovir based on renal function (CLcr) at the start of treatment in patients with symptomatic congenital CMV disease, the intended population of valganciclovir.

PMDA's view:

The applicant's explanation is acceptable. At present, the available data have shown no evident difference in plasma GCV concentration following administration of oral valganciclovir 16 mg/kg twice daily in patients with symptomatic congenital CMV disease, regardless of baseline renal function (CLcr).

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

The applicant submitted results from the clinical studies listed in Table 3 for efficacy and safety evaluation.

5) CLcr (mL/min/1.73 m^2) = k value[a)] × height (cm) / (serum creatinine level + 0.2[b)] [mg/dL])
a) If the body weight at birth is <2500 g, the k value is 0.33; if the body weight at birth is ≥2500 g, the k value is 0.45.
b) Since serum creatinine levels were determined using an enzymatic method in Study VGCV-1, the levels were converted into Jaffe method-based values.

Table 3. Outline of key clinical studies

Data type	Geographic region	Study identifier	Phase	Population	N	Dosage regimen	Main endpoints
Evaluation data	Japan	VGCV-1[a)]	III	Patients with symptomatic congenital CMV disease	25	Valganciclovir 16 mg/kg orally twice daily for 6 months	Efficacy Safety
Reference data	Foreign	CASG112	III	Patients with symptomatic congenital CMV disease	109	(1) 6-month treatment group Valganciclovir 16 mg/kg orally twice daily for 6 months (2) 6-week treatment group Valganciclovir 16 mg/kg orally twice daily for 6 weeks, followed by placebo orally twice daily until Month 6	Efficacy Safety
Reference data (Published article)	Foreign	CASG102	III	Patients with symptomatic congenital CMV disease	100	(1) GCV[b)] group GCV 6 mg/kg intravenously twice daily for 6 weeks (2) Untreated group	Efficacy Safety

a) The assessment period in Study VGCV-1 was until 1 month after the last dose of valganciclovir. A post-VGCV-1 observational study is ongoing to annually follow-up hearing loss, growth, development, etc. at ages from 1 to 6 years in patients participating in Study VGCV-1. As of [redacted], 20[redacted], interim data at up to 2 years of age are available from all patients in the observational study.
b) The active metabolite of valganciclovir

7.1 Japanese clinical study (CTD 5.3.5.2.1, Study VGCV-1, February 2020 to May 2021)

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of valganciclovir in patients with symptomatic congenital CMV disease (target sample size, 25 patients) [for the key inclusion/exclusion criteria, see Table 4].

Table 4. Key inclusion/exclusion criteria in Study VGCV-1

Inclusion criteria	1. Patients with congenital CMV disease in whom CMV nucleic acid was detected in urine via a CMV nucleic acid detection kit within 21 days of age 2. Patients with any of the following forms of CNS involvement: microcephaly, hydrocephalus/ventricular enlargement, periventricular calcification, cortical hypoplasia/white matter injury, chorioretinopathy, or abnormal auditory brainstem response (ABR) 3. Patients at ≤2 months of age at the time of giving consent 4. Patients who were born at a gestational age of ≥32 weeks 5. Patients who weigh ≥1800 g at the time of study enrollment
Exclusion criteria	1. Patients with bacterial infections requiring antibiotics 2. Patients with a serum creatinine level of >1.5 mg/dL 3. Patients with anencephaly or hydrocephalus due to other causes

Valganciclovir 16 mg/kg was administered orally twice daily for 6 months. Treatment interruption or dose reduction was allowed according to the decrease in neutrophil count or platelet count, or for other reasons [see Section 10.1].

Of the 25 enrolled patients, 24 received ≥1 dose of the study drug and were included in the safety analysis set and the full analysis set (FAS). The FAS served as the efficacy analysis set. Three patients discontinued the study treatment due to adverse events (neutrophil count decreased in 2 patients and neutropenia in 1 patient).

The median [95% confidence interval] change in whole blood CMV level from baseline to Month 6, the primary efficacy endpoint, was −246.0 [−905.0, −35.0][6)] IU/mL. In 100% (24 of 24) of the patients, the

6) Blood CMV levels that were below the detection limit were regarded as 1 IU/mL, for calculation of the change from baseline.

change[7)] in hearing loss level[8)] from baseline to Month 6 (best ear assessment[9)]), a key secondary endpoint, was classified as "improved," "no change (normal hearing)" or "no change (same degree of hearing loss)."

The incidence of adverse events[10)] was 79.2% (19 of 24 patients), while that of adverse drug reactions was 45.8% (11 of 24 patients). A list of adverse events and adverse drug reactions is presented in Table 5.

No adverse events resulted in death.

A serious adverse event, neutrophil count decreased, was reported in 4.2% (1 of 24) of patients, for which a causal relationship to the study drug could not be ruled out.

Adverse events led to treatment discontinuation in 33.3% (8 of 24) of patients (neutrophil count decreased in 5 patients, neutropenia in 2 patients, and anaemia in 1 patient). Of the 8 patients, 5 (neutrophil count decreased in 3 patients, neutropenia in 1 patient, and anaemia in 1 patient) resumed treatment with valganciclovir after the adverse events resolved.

Table 5. All adverse events and adverse drug reactions (safety analysis set)

Event	Adverse event	Adverse drug reaction	Event	Adverse event	Adverse drug reaction
Any event (N = 24)	19 (79.2)	11 (45.8)			
Dermatitis diaper	9 (37.5)	0	Otitis media	2 (8.3)	0
Neutrophil count decreased	8 (33.3)	8 (33.3)	Eczema	2 (8.3)	0
Constipation	5 (20.8)	0	Upper respiratory tract infection	1 (4.2)	0
Anaemia	4 (16.7)	1 (4.2)	Varicella	1 (4.2)	0
Eczema infantile	4 (16.7)	0	Balanoposthitis	1 (4.2)	0
Nasopharyngitis	4 (16.7)	0	Eczema asteatotic	1 (4.2)	0
Pyrexia	3 (12.5)	0	Erythema	1 (4.2)	0
Neutropenia	2 (8.3)	2 (8.3)	Miliaria	1 (4.2)	0
Impetigo	2 (8.3)	0	Rash	1 (4.2)	0
Skin candida	2 (8.3)	0	Urticaria	1 (4.2)	0

n (%), MedDRA Ver. 24.0

7.2 Foreign clinical study (Reference CTD 5.3.5.1.1, Study CASG112, June 2008 to May 2013)

A randomized, double-blind, parallel-group study was conducted in the US and the UK to evaluate the efficacy and safety of valganciclovir in patients with symptomatic congenital CMV disease (target sample size, 104 patients[11)]) [for the key inclusion/exclusion criteria, see Table 6].

7) The change in hearing loss level from baseline to the assessment point was classified into 4 grades: worsened, no change (normal hearing), no change (same degree of hearing loss), and improved. The change from baseline in distribution of the grades was assessed.

8) The hearing loss level was classified into 4 grades, according to auditory brainstem response (ABR): normal hearing, 0 to 20 dB; mild hearing abnormality, 21 to 45 dB; moderate hearing abnormality, 46 to 70 dB; and severe hearing abnormality, ≥71 dB.

9) The change in hearing loss level from baseline to each assessment point was assessed for right and left ears separately in each patient. The results of one ear with a better score than the other ear were used for the analysis.

10) Adverse events that occurred between the start of study treatment and 1 month after the end of treatment

11) Assuming that the expected proportions of patients in whom the change in hearing loss level from baseline to Month 6, the primary endpoint, were assessed as "improved by 3 levels," "improved by 2 levels," "improved by 1 level," "no change," and "worsened" are 5%, 10%, 35%, 50%, and 0%, respectively in the 6-month treatment group, and 0%, 4%, 16%, 75%, 5%, respectively in the 6-week treatment group, a sample size of 74 patients (37 per group) would provide a statistical power of 85% at a two-sided significance level of 5% in the Wilcoxon rank sum test. The sample size was increased to 104 patients (52 per group) to accommodate possible dropouts, etc.

The study consisted of an open-label phase and a double-blind phase. All enrolled patients received valganciclovir 16 mg/kg orally twice daily for 6 weeks (open-label phase). At the end of open-label phase, the patients were randomized to valganciclovir 16 mg/kg or placebo orally twice daily until Month 6 (double-blind phase[12)]). (Hereinafter, the group receiving valganciclovir in the double-blind phase is referred to as "the 6-month treatment group," while the group receiving placebo is referred to as "the 6-week treatment group"). Treatment interruption or dose reduction was allowed according to the decrease in neutrophil count or platelet count, or for other reasons [see Section 10.1].

Table 6. Key inclusion/exclusion criteria in Study CASG112

Inclusion criteria	1. Patients in whom CMV was detected from a urine or throat swab specimen via a culture, shell vial, or polymerase chain reaction (PCR) test 2. Patients with symptomatic congenital CMV disease, as manifested by any of the following: 1) thrombocytopenia, 2) petechiae, 3) hepatomegaly, 4) splenomegaly, 5) intrauterine growth restriction, 6) hepatitis (increased transaminase or bilirubin), or 7) CNS involvement of the CMV disease (e.g., microcephaly, radiographic abnormalities, abnormal cerebrospinal fluid, CMV DNA in the cerebrospinal fluid, chorioretinitis, and/or abnormal ABR) 3. Patients at ≤30 days of age at the time of study enrollment 4. Patients who were born at a gestational age of ≥32 weeks 5. Patients who weigh ≥1800 g at the time of study enrollment
Exclusion criteria	1. Patients who are receiving other antiviral agents or immunoglobulins 2. Patients with gastrointestinal abnormalities that may inhibit the absorption of oral drugs 3. Patients with renal insufficiency with a creatinine clearance of <10 mL/min/1.73 m^2 at the time of study enrollment

All 109 enrolled patients were included in the safety analysis set. In the safety analysis set, 96 patients (49 in the 6-week treatment group and 47 in the 6-month treatment group) completed the open-label phase and received ≥1 dose of the study drug in the double-blind phase. The 96 patients were included in the intent-to-treat (ITT) population, which served as the efficacy analysis set. Treatment discontinuation occurred in 11.9% (13 of 109) of patients in the open-label phase. The major reasons for discontinuation were consent withdrawal and noncompliance with the protocol.

As shown in Table 7, the change[13)] in hearing loss level[8)] (best ear assessment[14)]) from baseline to Month 6, the primary efficacy endpoint, did not statistically differ between the treatment groups.

Table 7. Changes in hearing loss level from baseline to Month 6 (best ear assessment) (ITT population)

Change from baseline in hearing loss level (best ear assessment)	6-month treatment (N = 43[a)])	6-week treatment (N = 43[a)])
Improved by 3 levels	0	0
Improved by 2 levels	0	0
Improved by 1 level	2 (4.7%)	3 (7.0%)
No change	36 (83.7%)	37 (86.0%)
Worsened	5 (11.6%)	3 (7.0%)
Wilcoxon rank sum test,[b)] P = 0.4051		

n (%)

a) Ten patients were excluded from the ITT population because their hearing loss levels could not be assessed at baseline or at Month 6 (4 in the 6-month treatment group and 6 in the 6-week treatment group).

b) Two-sided significance level of 5%

12) The double-blind phase continued even after the completion of scheduled duration of study treatment and was maintained until Month 24.

13) The change in hearing loss level from baseline to Month 6 was classified into 5 grades: worsened, no change, improved by 1 level, improved by 2 levels, and improved by 3 levels. The change from baseline in distribution of the grades was assessed.

14) The change in hearing loss level from baseline to each assessment point was assessed based on the results of one ear (left or right) with better hearing level than the other ear at baseline and each assessment point.

In the ITT population (96 patients),[15] the incidences of adverse events[16] were 95.7% (45 of 47 patients) in the 6-month treatment group and 98.0% (48 of 49 patients) in the 6-week treatment group. The incidences of adverse drug reactions were 40.4% (19 of 47 patients) in the 6-month treatment group and 42.9% (21 of 49 patients) in the 6-week treatment group. Common adverse events are listed in Table 8.

No deaths were reported.

Serious adverse events were reported in 23.4% (11 of 47) of patients in the 6-month treatment group (neutropenia in 3 patients, bronchiolitis and gastrooesophageal reflux disease in 2 patients each, and ankyloglossia congenital, otitis media, cough, diarrhoea haemorrhagic, anaemia, respiratory tract infection viral, feeding disorder neonatal, dehydration, vomiting, head injury, and respiratory syncytial virus infection in 1 patient each [some patients had more than one event]), and 38.8% (19 of 49) of patients in the 6-week treatment group (neutropenia in 8 patients, respiratory syncytial virus infection in 3 patients, anaemia in 2 patients, and bronchiolitis, dehydration, failure to thrive, gastroenteritis viral, gastrooesophageal reflux disease, otitis media, pneumonia, pyrexia, respiratory syncytial virus bronchiolitis, respiratory tract infection viral, and urinary tract infection in 1 patient each [some patients had more than one event]). A causal relationship to the study drug could not be ruled out in 2 patients in the 6-month treatment group (neutropenia in 2 patients and anaemia in 1 patient [1 patient had more than one event]) and 10 patients in the 6-week treatment group (neutropenia in 8 patients and anaemia in 2 patients).

Adverse events led to treatment discontinuation in 10.6% (5 of 47) of patients in the 6-month treatment group (neutropenia in 2 patients, and upper respiratory tract infection, feeding tube complication, and gastrooesophageal reflux disease in 1 patient each) and 8.2% (4 of 49) of patients in the 6-week treatment group (neutropenia in 3 patients and rash in 1 patient). Of the 9 patients, 8 resumed the study drug after the adverse events resolved, while the remaining 1 patient resumed the study drug although the event (rash) did not resolve.

[15] In 13 patients who failed to proceed to the double-blind phase (including 2 patients who were withdrawn before the start of study treatment), the incidences of adverse events and adverse drug reactions were 30.8% (4 of 13 patients) and 0% (0 of 13 patients), respectively.
[16] Events that occurred between the start of study treatment and 1 month after the end of treatment

Table 8. Adverse events and adverse drug reactions reported with a ≥5% incidence (safety analysis set)

Events	Adverse events		Adverse drug reactions	
	6-month treatment (N = 47)	6-week treatment (N = 49)	6-month treatment (N = 47)	6-week treatment (N = 49)
Any event	45 (95.7)	48 (98.0)	19 (40.4)	21 (42.9)
Upper respiratory tract infection	15 (31.9)	14 (28.6)	0	0
Neutropenia	12 (25.5)	17 (34.7)	10 (21.3)	15 (30.6)
Dermatitis diaper	11 (23.4)	4 (8.2)	0	0
Otitis media	11 (23.4)	12 (24.5)	0	0
Diarrhoea	9 (19.1)	13 (26.5)	1 (2.1)	3 (6.1)
Vomiting	9 (19.1)	6 (12.2)	1 (2.1)	2 (4.1)
Cough	8 (17.0)	4 (8.2)	0	0
Constipation	7 (14.9)	4 (8.2)	0	0
Oral candidiasis	7 (14.9)	6 (12.2)	0	0
Liver function test abnormal	6 (12.8)	4 (8.2)	3 (6.4)	4 (8.2)
Rash	6 (12.8)	11 (22.4)	0	0
Anaemia	5 (10.6)	11 (22.4)	2 (4.3)	8 (16.3)
Flatulence	5 (10.6)	8 (16.3)	0	1 (2.0)
Gastroenteritis	5 (10.6)	3 (6.1)	0	0
Gastrooesophageal reflux disease	5 (10.6)	10 (20.4)	0	1 (2.0)
Infantile colic	5 (10.6)	3 (6.1)	0	0
Conjunctivitis	4 (8.5)	4 (8.2)	0	0
Hypertonia	4 (8.5)	4 (8.2)	0	0
Nasal congestion	4 (8.5)	6 (12.2)	0	0
Bronchiolitis	3 (6.4)	3 (6.1)	0	0
Candidiasis	3 (6.4)	2 (4.1)	0	0
Ear infection	3 (6.4)	2 (4.1)	0	0
Pyrexia	3 (6.4)	9 (18.4)	0	0
Respiratory syncytial virus infection	3 (6.4)	3 (6.1)	0	0
Seborrhoeic dermatitis	3 (6.4)	1 (2.0)	0	0
Viral infection	3 (6.4)	0	0	0
Occult blood positive	2 (4.3)	3 (6.1)	0	0
Upper respiratory tract congestion	2 (4.3)	3 (6.1)	0	0
Hypotonia	1 (2.1)	4 (8.2)	0	0
Irritability	1 (2.1)	3 (6.1)	1 (2.1)	0
Partial seizures	1 (2.1)	3 (6.1)	0	0
Gastroenteritis viral	0	3 (6.1)	0	0
Head lag	0	3 (6.1)	0	0
Strabismus	0	3 (6.1)	0	0

n (%), MedDRA ver. 12.1

7.3 Foreign clinical study of GCV (Study CASG102, *J Pediatr.* 2003;143:16-25, *J Clin Virology.* 2009;46 Suppl 4:S22-6)

A randomized, open-label, comparative study was conducted in the US to evaluate the efficacy and safety of GCV (the active metabolite of valganciclovir) administered intravenously for 6 weeks versus no treatment with GCV in patients with symptomatic congenital CMV disease (target sample size, 100 patients) [for the key inclusion/exclusion criteria, see Table 9].

Table 9. Key inclusion/exclusion criteria in Study CASG102

Inclusion criteria	1. Patients with confirmed isolation of CMV from a urine specimen 2. Patients with symptomatic congenital CMV disease accompanied by CNS involvement, as manifested by any of the following:1) a CNS disorder such as microcephaly, 2) intracranial calcifications, 3) abnormal cerebrospinal fluid, 4) chorioretinitis, and/or 5) hearing loss 3. Patients at ≤1 month of age 4. Patients who were born at a gestational age of ≥32 weeks 5. Patients who weighed ≥1200 g at birth
Exclusion criteria	1. Patients receiving other antiviral agents or immunoglobulins 2. Patients with hydranencephaly 3. Patients with a serum creatinine level of >1.5 mg/dL

GCV 6 mg/kg was administered intravenously twice daily for 6 weeks. Treatment interruption or dose reduction was allowed according to the decrease in neutrophil count.[17)]

Of 100 enrolled patients, 97 (47 in the GCV group and 50 in the no-treatment group) were used for safety evaluation, and 42[18)] (25 in the GCV group and 17 in the no-treatment group) were used for efficacy evaluation (the primary endpoint).

The proportions of patients in whom the change[7)] in hearing loss level[8)] (best ear assessment[14)]) from baseline to Month 6 (the primary efficacy endpoint) was classified as "improved or no change (normal hearing)" were 84.0% (21 of 25 patients) in the GCV group and 58.8% (10 of 17 patients) in the no-treatment group.

The safety evaluation data reported:
Adverse events resulted in death in 3 patients in the GCV group (complications of CMV disease, and necrotizing enterocolitis and cardio-respiratory arrest in 1 patient each) and 6 patients in the no-treatment group (sudden infant death syndrome, pneumonia, necrotizing enterocolitis, candida septicemia, dehydration, and *Escherichia* sepsis in 1 patient each). All of these events were unrelated to the study drug.

Grade 3 or 4 neutropenia was reported in 63% (29 of 46) of patients in the GCV group and 21% (9 of 43) of patients in the non-treatment group; 14 patients in the GCV group required dose reduction and 4 patients discontinued treatment.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and design of the Japanese investigator-initiated clinical study

The applicant explained the clinical data package for valganciclovir for the treatment of symptomatic congenital CMV disease:

The applicant's explanation:
When the development of valganciclovir started in Japan, the foreign clinical studies (Studies CASG112 and CASG102) had already been conducted, and the treatment guidelines by the International Congenital Cytomegalovirus Recommendations Group and the European Society of Paediatric Infectious Diseases (*Lancet Infect Dis.* 2017;17:e177-88 and *Pediatr Infect Dis J.* 2017;36:1205-13) recommended pharmacotherapy with valganciclovir for patients with moderate to severe symptomatic congenital CMV disease [see Section 1]. Although no drugs had been approved for symptomatic congenital CMV disease either in or outside of Japan, conducting a placebo-controlled study was considered infeasible, because symptomatic congenital CMV

[17)] If the neutrophil count decreases to <500/mm^3 after the start of study treatment, the study drug should be interrupted; and if it recovers to ≥750/mm^3, the study drug may be resumed at the specified dose. If the neutrophil count again decreases to <500/mm^3, the dose of study drug should be reduced by 50% until it recovers to ≥500/mm^3. If the decrease in neutrophil count persists after the dose reduction, the study drug should be discontinued.
[18)] Of the 100 patients enrolled in the study, 58 were excluded from the efficacy (the primary endpoint) analysis because they did not undergo ABR-based hearing loss assessment at baseline or Month 6.

disease may lead to serious outcomes such as sensorineural hearing loss, mental retardation, and movement disorder, along with the above-mentioned background.

Taking these points into account, together with the facts mentioned below, the applicant considered that the efficacy and safety of valganciclovir in Japanese patients with symptomatic congenital CMV disease could be evaluated by conducting a Japanese Study VGCV-1 using a dosage regimen of valganciclovir, inclusion criteria, endpoints, etc. largely similar to those used in the foreign Study CASG112, and by assessing the similarity of the clinical study results between the Japanese study and the foreign study.

- No clinically significant ethnic differences in the PK of valganciclovir had been noted between the Japanese and non-Japanese populations [see Section 6.R.1].
- According to treatment guidelines and published reports,[19] the diagnostic method, disease conditions, and epidemiology of symptomatic congenital symptomatic CMV disease were considered to be similar in and outside of Japan, as mentioned below.
  - Both in and outside of Japan, symptomatic congenital CMV disease is definitively diagnosed by CMV nucleic acid detection using a specimen (e.g., urine) from neonates aged ≤3 weeks.
  - No differences have been reported with regard to the major manifestations of symptomatic congenital CMV disease (e.g., microcephaly, hydrocephalus, cerebral ventriculomegaly, sensorineural hearing loss, hepatic disorder, and chorioretinopathy) or the symptoms of neurologic sequelae (e.g., sensorineural hearing loss, mental retardation, and movement disorder) between Japanese and non-Japanese patients. The incidences of neurologic sequelae in patients with symptomatic congenital CMV disease were largely similar in these populations (40%-90%).

In addition, hearing loss has been known to be a major clinical manifestation and serious sequela of symptomatic congenital CMV disease. Inhibition of the deterioration of hearing loss by valganciclovir was selected as the primary efficacy endpoint in both the Japanese and foreign studies, because inhibiting hearing deterioration and maintaining hearing can affect the improvement of the patient's developmental outcomes and quality of life (*J Pediatr.* 2003;143:16-25), and because ABR hearing testing can yield objective assessment results even in neonates and infants. In addition, the following were to be also evaluated: (a) the effect of valganciclovir on developmental retardation, a known serious sequela of symptomatic congenital CMV disease, and (b) the antiviral effect of valganciclovir.

PMDA's view:

In light of the above explanation of the applicant, together with the fact that symptomatic congenital CMV disease is a rare disease, there was no choice but to conduct Study VGCV-1 as an open-label, uncontrolled study. PMDA thus reviewed the efficacy and safety of valganciclovir based on the submitted clinical study results.

[19] *Lancet Infect Dis.* 2017;17:e177-88, *Pediatr Infect Dis J.* 2017; 36:1205-13, *Rev Med Virol.* 2007; 17:355-63, *J Pediatr.* 2014; 164:855-9, Investigation on the effects of prenatal education for the prevention of congenital cytomegalovirus disease; study on the structure of the pregnant and neonatal screening system and the identification of disease risks in infected neonates [in Japanese] (last accessed on May 16, 2022; https://www.med.kobe-u.ac.jp/cmv/new_results.html), and *The Journal of Pediatric Infectious Diseases and Immunology.* 2010;22:385-9

7.R.2 Efficacy

7.R.2.1 Inhibition of deterioration of hearing loss

The applicant's explanation:

Table 10 presents the assessment methods for hearing loss level used in Studies VGCV-1, CASG112, and CASG102.

Table 10. Definitions in the assessment methods for hearing loss level

Study	Study VGCV-1 and the subsequent observational study	Study CASG112	Study CASG102
Assessment method for hearing loss level	The hearing loss level at each assessment point was classified based on ABR into 4 grades: normal hearing (0-20 dB), mild impairment (21-45 dB), moderate impairment (46-70 dB), and severe impairment (≥71 dB).		
Assessment method for the change from baseline in hearing loss level[a)]	The change in hearing from baseline to each assessment point was classified into 4 grades: improved, no change (normal hearing), no change (same degree of hearing loss), and worsened. The effect of valganciclovir was assessed based on the proportions of patients with each grade.		
		The change in hearing loss level from baseline to Month 6 was classified into 5 grades: "worsened," "no change," "improved by 1 grade," "improved by 2 grades," and "improved by 3 grades." The effect of valganciclovir was assessed based on the proportions of patients with each grade.	
Analysis using a best ear assessment	The change in hearing loss level from baseline to each assessment point was assessed for right and left ears separately in each patient. The results of one ear with a better score than the other ear were used for the analysis.	The change in hearing loss level from baseline to each assessment point was assessed based on the results of one ear (left or right) with better hearing level than the other ear at baseline and each assessment point. (Unlike in Study VGCV-1, the ear [left or right] assessed at baseline may be different from the ear assessed at each assessment).	

a) In Study CASG112, changes in hearing loss level from baseline to each assessment point were assessed using a 4-grade scale and a 5-grade scale. The primary endpoint was analyzed based on the 5-grade scale results and the secondary endpoints based on the 4-grade scale results.

Table 11 shows the change (best ear assessment) in hearing loss level from baseline to Month 6 of treatment with valganciclovir or GCV, as assessed on a 4-grade scale, in Studies VGCV-1, CASG112, and CASG102.

The proportions of patients classified as "(4) worsened" were lower in the valganciclovir or GCV group (0%-11.6%) than in the non-treatment group of Study CASG102 (41.2% [7 of 17 patients]). In Study CASG112, the prolongation of treatment duration from 6 weeks to 6 months showed no clear difference in inhibition of the deterioration of hearing loss by valganciclovir. Among patients participating in the ongoing post-VGCV-1 observational study (hereinafter referred to as "observational study patients"), the change from baseline in hearing loss level (best ear assessment) was classified as "(4) worsened" in 8.3% (2 of 24) of patients at 1 year of age and 0% (0 of 24) of patients at 2 years of age; these results showed no marked deterioration of hearing loss.

Based on these study results, valganciclovir is expected to have a certain level of efficacy in inhibiting the deterioration of hearing loss.

Table 11. Changes (best ear assessment) in hearing loss level from baseline to Month 6

Study identifier	Study VGCV-1	Study CASG112		Study CASG102	
Study drug	Valganciclovir	Valganciclovir	Valganciclovir	GCV	No treatment
Dosage regimen (Duration of treatment)	16 mg/kg twice daily (6 months)	16 mg/kg twice daily (6 months)	16 mg/kg twice daily (6 weeks)	6 mg/kg twice daily (6 weeks)	No treatment
N	24	43	43	25	17
(1) Improved	14 (58.3)	2 (4.7)	3 (7.0)	6 (24.0)	5 (29.4)
(2) No change (normal hearing)	4 (16.7)	28 (65.1)	23 (53.5)	15 (60.0)	5 (29.4)
(3) No change (same degree of hearing loss)	6 (25.0)	8 (18.6)	14 (32.6)	4 (16.0)	0
(4) Worsened	0[a)]	5 (11.6)	3 (7.0)	0	7 (41.2)
(1) + (2)	18 (75.0)	30 (69.8)	26 (60.5)	21 (84.0)	10 (58.8)

n (%)

a) A post-hoc assessment, which used the same best ear assessment as that used in Studies CASG112 and CASG102, again yielded a result of zero.[20)]

PMDA's view:

There is limitation of interpreting the study results because the results of different studies were compared, but the above explanation of the applicant is understandable to a certain extent. PMDA concluded that ≥6 week treatment with valganciclovir is expected to inhibit the deterioration of hearing loss in patients with symptomatic congenital CMV disease. However, Study CASG112 showed no clear difference in inhibition of the deterioration of hearing loss between the 6-week treatment and the 6-month treatment. Therefore, the duration of treatment with valganciclovir will be discussed in Section 7.R.6, taking also into account the reviews of other efficacy findings [see Sections 7.R.2.2 and 7.R.2.3] and safety [see Section 7.R.3] of valganciclovir.

7.R.2.2 Effects on development

The applicant's explanation:

In Study CASG102, Denver II Developmental Screening Test[21)] was performed at Month 6 and Month 12 after the start of treatment in an open-label manner. The results showed that the mean "number of developmental delays" was lower in the GCV group than in the non-treatment group at both Month 6 (4.46 in the GCV group and 7.51 in the no-treatment group) and Month 12 (10.06 in the GCV group and 17.14 in the no-treatment group).

In Study CASG112, development was assessed by Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III)[22)] at Month 12 and Month 24 in a double-blind manner [Table 12]. The 6-month treatment group had higher scores in any test than the 6-week treatment group, suggesting a trend that the 6-month treatment with valganciclovir provided greater improvement in developmental outcomes.

20) The results of 2 patients were changed: from (1) Improved to (2) No change (normal hearing) in one patient; and from (1) Improved to (3) No change (same degree of hearing loss) in the other.

21) A developmental test to assess the degree of relative development in infants/children. The test addresses 4 domains: "personal-social," "fine motor," "language," and "gross motor." For each test item, the behavior of a child was classified as "caution" (unable to complete an item that can be completed by 75%-90% of their age-matched children) or "delay" (unable to complete an item that can be completed by ≥90% of their age-matched children). The total number of "delays" per child was defined as "the number of developmental delays."

22) A comprehensive developmental scale consisting of (a) cognitive, language, and motor tests administered to individuals children and (b) questionnaires completed by caregivers concerning their children's socio-emotional and adaptive behaviors. The developmental scale is composed of the cognitive composite score (receptive and expressive communication scores), language composite score, and motor composite score (fine and gross motor scores). Each composite score ranges from 40 to 160, with higher scores suggesting a better developmental outcome.

Table 12. Developmental assessments at Month 12 and Month 24 in Study CASG112

Assessment point	Month 12			Month 24		
Treatment group	6-month treatment	6-week treatment	Between-group difference in the mean composite score[a)]	6-month treatment	6-week treatment	Between-group difference in the mean composite score[a)]
Cognitive composite score at each assessment point						
N	43	45	-	42	41	-
≥100	15 (34.9)	9 (20.0)	10.3	5 (11.9)	4 (9.8)	7.8
≥85 and <100	12 (27.9)	10 (22.2)		16 (38.1)	13 (31.7)	
≥70 and <85	4 (9.3)	9 (20.0)		8 (19.0)	6 (14.6)	
<70	12 (27.9)	17 (37.8)		13 (31.0)	18 (43.9)	
Language composite score at each assessment point						
N	41	43	-	41	41	-
≥100	7 (17.1)	4 (9.3)	10.5	8 (19.5)	5 (12.2)	11.5
≥85 and <100	15 (36.6)	11 (25.6)		11 (26.8)	10 (24.4)	
≥70 and <85	7 (17.1)	14 (32.6)		7 (17.1)	6 (14.6)	
<70	12 (29.3)	14 (32.6)		15 (36.6)	20 (48.8)	
Motor composite score at each assessment point						
N	42	44	-	41	40	-
≥100	3 (7.1)	7 (15.9)	9.1	6 (14.6)	6 (15.0)	11.4
≥85 and <100	18 (42.9)	9 (20.5)		14 (34.1)	9 (22.5)	
≥70 and <85	8 (19.0)	5 (11.4)		11 (26.8)	8 (20.0)	
<70	13 (31.0)	23 (52.3)		10 (24.4)	17 (42.5)	

n (%)

a) A generalized linear model including CNS disorder status at baseline as a covariate

Table 13 shows the results of developmental assessment (total developmental quotient [DQ]) using the Kyoto scale of psychological development[23)] at 1 and 2 years of age in the observational study patients. No clinical study results are available that compare different durations of valganciclovir therapy in Japanese patients with symptomatic congenital CMV disease. Therefore no definitive conclusion can be drawn, but a 6-month treatment with valganciclovir is likely to decrease the proportion of patients classified as "delayed (total DQ of <70)," in view of the following finding:

In a Japanese study, 43% (9 of 21) of patients who received valganciclovir 32 mg/kg/day (same as the proposed dosage) for approximately 6 weeks[24)] were classified as "delayed (total DQ of <70)" at a corrected age of 18 months (*Brain Dev.* 2019;41:743-50).

Table 13. Developmental assessment at 1 and 2 years of age in the observational study patients (total DQ)

Assessment point		1 year of age	2 years of age
N		24	24
Total DQ	Normal (≥85)	13 (54.2)	14 (58.3)
	Borderline (≥70 and <85)	4 (16.7)	4 (16.7)
	Delayed (<70)	7 (29.2)	6 (25.0)

n (%)

PMDA's view:

The applicant's explanation is understandable to a certain extent, and PMDA considers that a 6-month treatment with valganciclovir is likely to inhibit developmental delay. However, since only limited data are available on long-term developmental outcomes in patients treated with valganciclovir for symptomatic

23) A test to assess the developmental level of a child by comparing his/her behavior and response with those of age-matched children. The developmental level is assessed based on 3 domains: the postural-motor domain, the cognitive-adaptive domain, and the language-social domain. Using the test results, the following are calculated: (a) a developmental age, which expresses the child's developmental level and (b) a developmental quotient (DQ), which is the ratio of the developmental age to the child's chronological age (developmental age/chronological age × 100). Children with a DQ of ≥85 were classified as "normal," those with a DQ of ≥70 to <85 as "borderline," and those with a DQ of <70 as "delayed."

24) The duration of treatment with valganciclovir in Japanese patients with symptomatic congenital CMV disease (21 evaluable patients) was 6 weeks in 76% (16 of 21) of patients and 6 months in 24% (5 of 21) of patients.

congenital CMV disease, the applicant should continue to collect information in the post-marketing setting, and appropriately communicate the obtained information to healthcare professionals.

7.R.2.3 Antiviral effect

The applicant's explanation:

Figures 1 and 2 show the changes over time in whole blood CMV levels in Studies VGCV-1 and CASG112, respectively, in patients with symptomatic congenital CMV disease.

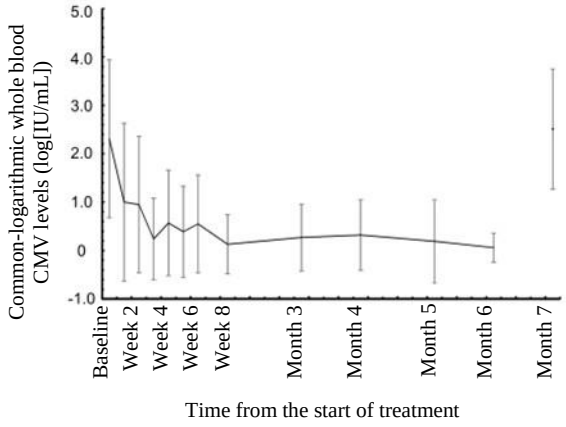

Figure 1. Changes over time in whole blood CMV levels in Study VGCV-1
(mean ± SD) (FAS)

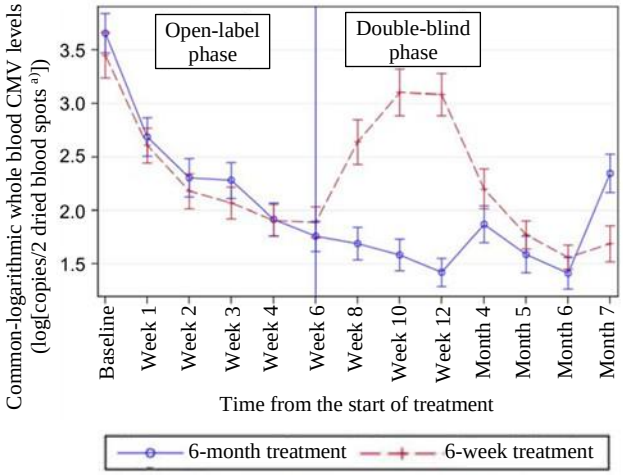

Figure 2. Changes over time in whole blood CMV levels in Study CASG112
(mean ± SE) (ITT population)
a) Each dried blood spot was defined as having a diameter of 3 mm (*JAMA.* 2010;303:1375-82).

The whole blood CMV level decreased during treatment with valganciclovir and rebounded after the completion of treatment. However, the rebounded CMV levels are considered to spontaneously normalize with the growth of the patients as their immune systems develop, in view of the report that CMV in patients with congenital CMV disease spontaneously decreases or disappears over time (e.g., *J Clin Virol.* 1999;14:57-66, *Pediatric Infect Dis Soc.* 2016;5:14-20, etc.).

PMDA's view:

The antiviral effect of valganciclovir against CMV disease is already known, and the antiviral effect of valganciclovir against CMV can be expected also in patients with symptomatic congenital CMV disease. Although a rebound in whole blood CMV level was noted after the completion of treatment with valganciclovir, the applicant's explanation that the rebounded whole blood CMV levels are expected to spontaneously normalize with the growth of the patients as their immune systems develop, is understandable.

Based on the above review in Section 7.R.2, PMDA concluded that valganciclovir was expected to have efficacy in Japanese patients with symptomatic congenital CMV disease. However, since only limited data are available on the long-term outcomes in Japanese patients treated with valganciclovir for symptomatic

congenital CMV disease, the applicant should continue to collect information in the post-marketing setting, and appropriately communicate the obtained information to healthcare professionals.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.3 Safety

7.R.3.1 Summary of safety

The applicant's explanation:

Table 14 presents a summary of the safety of valganciclovir in the Japanese and foreign studies (Studies VGCV-1 and CASG112).

Table 14. Summary of the safety of valganciclovir in the Japanese and foreign studies (safety analysis set)

Study	Study VGCV-1	Study CASG112	
Treatment group	6-month treatment (N = 24)	6-month treatment (N = 47)	6-week treatment (N = 49)
Adverse events	19 (79.2)	45 (95.7)	48 (98.0)
Adverse drug reactions	11 (45.8)	19 (40.4)	21 (42.9)
Adverse events resulting in death	0	0	0
Adverse drug reactions resulting in death	0	0	0
Serious adverse events	1 (4.2)	11 (23.4)	19 (38.8)
Serious adverse drug reactions	1 (4.2)	2 (4.3)	10 (20.4)

n (%)

In Study VGCV-1, bone marrow depression-related adverse events were most commonly reported. The serious adverse event was neutrophil count decreased in 4.2% (1 of 24) of patients. Adverse events that led to treatment discontinuation were neutrophil count decreased (20.8% [5 of 24 patients]), neutropenia (8.3% [2 of 24 patients]), and anaemia (4.2% [1 of 24 patients]). Also in the 6-month treatment group of Study CASG112 (which used the same dosage regimen as that in Study VGCV-1), bone marrow depression-related adverse events were commonly reported; common serious adverse events included neutropenia (6.4% [3 of 47 patients]), bronchiolitis (4.3% [2 of 47 patients]) and gastrooesophageal reflux disease (4.3% [2 of 47 patients]). Thus, the trend of occurrence of adverse events in Study CASG112 was largely similar to that in Study VGCV-1. In Study CASG112, the incidences of adverse events and serious adverse events did not increase in the 6-month treatment group as compared with the 6-week treatment group.

The following number of serious events were reported spontaneously according to the post-marketing safety information collected between November 5, 2004[25)] and December 7, 2022 in and outside of Japan (estimated number of treated patients, approximately 1,570,000 patients[26)]):

- 278 events in patients aged <9 months of age (including those reported to be 0 years old)
- 12,931 events in patients aged ≥9 months
- 4,767 events in patients of unknown age category.

[25)] Including the information obtained in 1998 from 1 patient with CMV retinitis (who switched from GCV therapy to valganciclovir therapy in a clinical study)

[26)] This number was estimated based on the cumulative number of valganciclovir shipments between the foreign initial approval date (March 2001) and March 2022, as well as other data.

Among the 278 serious events spontaneously reported from patients with symptomatic congenital CMV disease aged <9 months (i.e., the intended population of valganciclovir therapy), the following were reported with an incidence of ≥5 events: neutropenia (42 events), neutrophil count decreased (14 events), anaemia (13 events), agranulocytosis and seizure (7 events each), hyperkalaemia (6 events), and CMV infection and cholestasis (5 events each). All of these events were also reported from a certain number of patients aged ≥9 months, and no safety concerns specific to patients aged <9 months have been reported.

As mentioned above, no new safety concerns specific to neonates or infants have been identified in Japanese and foreign studies involving patients with symptomatic congenital CMV disease or the post-marketing safety information for valganciclovir. Further, the plasma GCV exposure ($AUC_{0\text{-}24h}$) in patients with symptomatic congenital CMV disease who received valganciclovir at the proposed dosage and administration was similar to that observed in pediatric solid organ transplant recipients (an approved indication) receiving valganciclovir at the approved dosage and administration [see Section 6 R.1]. In view of these facts and other findings, the risks associated with the use of valganciclovir in patients with symptomatic congenital CMV disease are considered to be manageable by issuing an adequate caution statement similar to those regarding the safety of valganciclovir administered for the approved indications, and by ensuring careful administration of valganciclovir.

PMDA's view:
PMDA confirmed that the safety risks associated with the use of valganciclovir in patients with symptomatic congenital CMV disease are not higher than those for the approved indications.

7.R.3.2 Monitoring of bone marrow depression-related events

The applicant's explanation:
Most of the bone marrow depression-related adverse events occurred within 2 months (60 days) after the start of treatment with valganciclovir in Studies VGCV-1 and CASG112. Therefore, hematology tests during the early days of treatment with valganciclovir are important. Given the frequencies of visits and hematology tests in Studies VGCV-1[27)] and CASG112,[28)] medical examinations and hematology tests should be performed once weekly or every 2 weeks for the first 2 months of treatment with valganciclovir, and at least once monthly thereafter. The bone marrow depression-related events occurring in Studies VGCV-1 and CASG112 resolved by a dose reduction or interruption of valganciclovir and by administration of G-CSF or other appropriate therapeutic actions [See Section 10.1]. Therefore, the risks associated with valganciclovir in patients with symptomatic congenital CMV disease are considered to be manageable by conducting periodic hematology tests during valganciclovir therapy (which has already been recommended for the approved indications) and by reducing the dose or interrupting valganciclovir appropriately after the occurrence of bone marrow depression-related events.

27) Hematology tests were conducted once weekly between the start of valganciclovir therapy and Week 6; once at Week 8; and once monthly afterward until 1 month after the end of treatment.
28) Hematology tests were conducted once weekly between the start of valganciclovir therapy and Week 4; then once every 2 weeks until Week 12; and once monthly afterward until 1 month after the end of treatment.

PMDA's view:

PMDA accepted the applicant's explanation and concluded that the applicant should inform users of valganciclovir about the recommended frequency of visits/testing through information materials, etc., to ensure that bone marrow depression-related adverse drug reactions of valganciclovir in patients with symptomatic congenital CMV disease are appropriately managed.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

PMDA concluded that the following applicant's explanation about the clinical positioning of valganciclovir was acceptable.

The applicant's explanation: Based on the foreign treatment guidelines for symptomatic congenital CMV disease and the results from the Japanese clinical study, valganciclovir therapy should be recommended for patients with symptomatic congenital CMV disease accompanied by non-transient laboratory abnormalities requiring treatment, CNS involvement, or other symptoms, as recommended by the foreign treatment guidelines [Table 1].

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.5 Indication

PMDA's view:

In view of the results of the reviews in Sections 7.R.2 to 7.R.4, PMDA concluded that the indication of valganciclovir should be "treatment of symptomatic congenital CMV disease," and the "Precautions Concerning Indications" section of the package insert should include a statement that valganciclovir therapy should be recommended for patients with symptomatic congenital CMV disease accompanied by laboratory abnormalities requiring treatment, CNS involvement, or other symptoms. By means of post-marketing surveillance, etc., the applicant should collect the efficacy and safety data of valganciclovir in patients with symptomatic congenital CMV disease without CNS involvement who have laboratory abnormalities requiring treatment, because such patients were not enrolled in the Japanese clinical study; the applicant should promptly communicate new findings to healthcare professionals if they become available.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.6 Dosage and administration

PMDA's view:

In view of the results of the reviews in Sections 6.R.1 (dosage regimens selected in the clinical studies) and 6.R.2 (effects of renal function on the PK of valganciclovir), 7.R.2 (efficacy), and 7.R.3 (safety), PMDA concluded that the dosage and administration of valganciclovir in the treatment of symptomatic congenital

CMV disease can be set at 16 mg/kg administered orally twice daily. Although the prolongation of treatment duration from 6 weeks to 6 months showed no clear difference in inhibition of the deterioration of hearing loss in Study CASG112 [see Section 7.R.2.1], the "Precautions Concerning Dosage and Administration" section of the package insert should state that valganciclovir should be administered for 6 months as the standard of treatment duration, for the following reasons:

- Results from Study CASG112 and other data have suggested that the incidence of developmental delay is likely to be reduced by a 6-month treatment with valganciclovir, as compared with a 6-week treatment [see Section 7.R.2.2].
- Results from Study CASG112 and other data showed the decrease in whole blood CMV level during treatment with valganciclovir [see Section 7.R.2.3]. CNS involvement in patients with congenital CMV disease is caused partly by viral effects on the differentiation/proliferation of human fetal neuroepithelial progenitors (*J Neurosci Res.* 2005;82:839-50); the longer blood CMV remains at low levels during the period when the nerves develop dramatically, the more likely the deterioration of CNS impairment will be inhibited.
- Results from nonclinical studies have suggested a carcinogenic risk associated with the long-term use of valganciclovir, but the incidences of adverse events, serious adverse events, etc. did not clearly differ between the 6-month treatment group and the 6-week treatment group in Study CASG112 [see Section 7.R.3].

However, there is no available information on the PK or safety of valganciclovir administered to patients with symptomatic congenital CMV disease accompanied by renal impairment. Since the major elimination route of GCV is renal excretion, these patients are likely to experience an increase in plasma GCV concentration. Therefore, the applicant should issue a precautionary statement to the following effect:

When administering valganciclovir to patients with symptomatic congenital CMV disease accompanied by renal impairment, their symptoms and blood test results relating to bone marrow depression should be monitored carefully, and appropriate actions (e.g., dose reduction or discontinuation of valganciclovir) should be taken if necessary.

In the post-marketing setting, the applicant should continue to collect the safety data of valganciclovir administered to patients with symptomatic congenital CMV disease accompanied by renal impairment from the published literature and other sources, and should promptly communicate new findings to healthcare professionals if they become available.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant plans to conduct post-marketing surveillance to collect following information:

- The safety of valganciclovir administered in clinical practice and the long-term outcomes of neurological sequelae (e.g., sensorineural hearing loss, mental retardation, and movement disorder) in patients treated with valganciclovir for symptomatic congenital CMV disease

PMDA's view:

In the post-marketing setting, the applicant should continue to collect the following information from the published literature and other sources: (a) the efficacy and safety data of valganciclovir in patients with symptomatic congenital CMV disease without CNS involvement who have laboratory abnormalities requiring treatment; and (b) the safety data of valganciclovir in patients with symptomatic congenital CMV disease accompanied by renal impairment. The applicant should promptly communicate new findings to healthcare professionals if they become available.

The above conclusion by PMDA will be discussed at the Expert Discussion.

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 the document-based GLP/GCP inspections and data integrity assessment

The inspections are currently ongoing. The results and the conclusion of PMDA will be reported in the Review Report (2).

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

The inspection is currently ongoing. The results and the conclusion of PMDA will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that valganciclovir has efficacy in the treatment of symptomatic congenital CMV disease, and that valganciclovir has acceptable safety in view of its benefits. Valganciclovir is clinically meaningful because it offers a new treatment option for patients with symptomatic congenital CMV disease.

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

10. Others

10.1 Criteria for interruption, dose reduction, and discontinuation of the study drug in the clinical studies

Table 15 presents the criteria for the interruption, dose reduction, and discontinuation of the study drug in the Japanese and foreign clinical studies (Studies VGCV-1 and CASG112).

Table 15. Key criteria for the interruption, dose reduction, and discontinuation of the study drug in the Japanese and foreign clinical studies

	Study VGCV-1	Study CASG112
Neutrophil count decreased		
Interruption criteria	If the neutrophil count decreases to <500/mm^3 after the start of study treatment, the study drug should be interrupted. If it subsequently recovers to ≥750/mm^3, the study drug may be resumed at the specified dose.	If the neutrophil count decreases to ≤500/mm^3 twice or more within 1 week after the start of study treatment, the study drug should be interrupted. If it subsequently recovers to >750/mm^3, the study drug may be resumed at the specified dose.
Dose reduction criteria	If the neutrophil count again decreases to <750/mm^3, the dose of study drug should be reduced by 50%.	If the neutrophil count again decreases to ≤750/mm^3 within 1 week, the dose of study drug should be reduced by 50%.
Discontinuation criteria	If the neutrophil count decreases to <500/mm^3 at the reduced dose, the study drug should be discontinued.	If the neutrophil count decreases to ≤500/mm^3 at the reduced dose within 1 week, the study drug should be discontinued.
Platelet count decreased		
Interruption criteria	If the platelet count decreases to <50,000/mm^3 after the start of study treatment, the study drug should be interrupted. If it subsequently recovers to ≥50,000/mm^3, the study drug may be resumed at the specified dose.	If the platelet count decreases to ≤50,000/mm^3 (or ≤50% of the baseline level) twice or more within 1 week after the start of study treatment, the study drug should be interrupted. If it subsequently recovers to ≥50,000/mm^3 (or >50% of the baseline level), the study drug may be resumed at the specified dose.
Haemoglobin decreased		
Interruption criteria	If the haemoglobin level falls to <8 g/dL after the start of study treatment, the study drug should be interrupted. If it subsequently recovers to ≥8 g/dL, the study drug may be resumed at the specified dose.	None
Increased liver function test results		
Interruption criteria	If the AST or ALT level increases to ≥10 times the baseline level (or ≥500 U/L), the study drug should be interrupted. If it subsequently recovers to <10 times the baseline level (or <500 U/L), the study drug may be resumed at the specified dose.	If the ALT level increases to >10 times the baseline level twice or more within 1 week after the start of study treatment, the study drug should be interrupted. If it subsequently recovers to <5 times the baseline level, the study drug may be resumed.
Discontinuation criteria	If the AST or ALT level again increases to ≥10 times the baseline level (or ≥500 U/L), the study drug should be discontinued.	If the ALT level again increases to >10 times the baseline level, the study drug should be discontinued.

Review Report (2)

February 15, 2023

Product Submitted for Approval

Brand Name	Valixa Dry Syrup 5000 mg
Non-proprietary Name	Valganciclovir Hydrochloride
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	June 30, 2022

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy, safety, clinical positioning, indication, dosage and administration, post-marketing investigations, and risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusions regarding the issues described in the Review Report (1) [Sections "7.R.2 Efficacy," "7.R.3 Safety," "7.R.4 Clinical positioning," "7.R.5 Indication," "7.R.6 Dosage and administration," and "7.R.7 Post-marketing investigations"], while making the following comment.

- Since only limited data are available on the long-term outcomes of treatment with valganciclovir in patients with symptomatic congenital CMV disease, relevant information should be appropriately collected in the post-marketing setting and obtained information should be appropriately communicated to healthcare professionals.

Based on the review described in the Section "7.R.7 Post-marketing investigations" of the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA concluded that the applicant should include the safety and efficacy specifications presented in Table 16 in the risk management plan (draft), and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and risk minimization activities presented in Table 17 as well as routine pharmacovigilance practice. PMDA then instructed the applicant to conduct post-marketing surveillance, etc. that covers these issues.

Table 16. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Bone marrow depression, pancytopenia, aplastic anaemia, leucopenia, neutropenia, anaemia, and thrombocytopenia • Serious haemorrhage due to thrombocytopenia (including gastrointestinal haemorrhage) • Renal failure • Pancreatitis • Deep thrombophlebitis • Convulsion, psychotic disorder, hallucination, confusion, agitation, and coma • Infection relating to bone marrow disorder or immune system disorder, such as sepsis.	• Teratogenic, genotoxic, and carcinogenic potentials • Spermatogenic disorder	• None
Efficacy specification		
• Long-term outcomes of neurological sequelae (e.g., sensorineural hearing loss, mental retardation, and movement disorder)		

Table 17. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Specified use-results survey (long-term efficacy and safety of valganciclovir in clinical practice)		• Organize and disseminate information material (a proper use guide of valganciclovir) for healthcare professionals • Organize and disseminate information material for patients' guardians

The applicant's explanation:

A specified use-results survey, summarized in Table 18, will be implemented in patients with symptomatic congenital CMV disease to evaluate the long-term efficacy and safety of valganciclovir in clinical practice.

PMDA accepted the applicant's explanation.

Table 18. Outline of the specified use-results survey (draft)

Objective	To assess the long-term outcomes of neurological sequelae (e.g., sensorineural hearing loss, mental retardation, and movement disorder) after treatment with valganciclovir and the safety of valganciclovir in clinical practice
Survey method	Central registry system
Population	Patients treated with valganciclovir for symptomatic congenital CMV disease
Survey period (Registration period)	5 years (4 years)
Observation period	1 year after the start of treatment with valganciclovir
Planned sample size	65 patients
Main survey items	Patient characteristics, maternal characteristics, details of treatment, hearing (auditory brainstem response [ABR]), hearing (behavioral observation audiometry [BOA], only at institutions unable to conduct ABR or in patients unable to undergo ABR), blood CMV level, mental/motor development (Enjoji infantile developmental scale), growth (height, body weight, head circumference), presence or absence of ophthalmologic abnormalities, laboratory results, etc. (platelet count, white blood cell count, hemoglobin, AST, ALT), and safety (e.g., the implementation status, etc. of bone marrow depression-related laboratory tests/treatments)

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

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

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

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

The new drug application data (CTD 5.3.5.2.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The clinical study was generally performed in accordance with GCP. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the inspection revealed the following findings associated with the sponsor-investigator although they have minor impact on the overall assessment of the study. The sponsor-investigator was notified of the findings and was instructed to take corrective actions.

Findings requiring corrective actions

Sponsor-investigator

- Improper descriptions were found in the contract to outsource part of the study-related duties.
- Part of information on adverse drug reactions, etc. was not collected.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as follows, with the approval condition shown below. The product has been designated as an orphan drug for the proposed indication. Accordingly, the re-examination period for the indication and dosage and administration for the present application should be 10 years.

Indications

Cytomegalovirus disease in the following patients:

- Patients with acquired immunodeficiency syndrome
- Organ transplant recipients (including hematopoietic stem cell transplant recipients)
- Patients with malignant tumors

Prevention of cytomegalovirus disease in organ transplant recipients (excluding hematopoietic stem cell transplant recipients)

~~Treatment of~~ Symptomatic congenital cytomegalovirus disease

(The strikethrough denotes deletions from the proposed text.)

Dosage and Administration

Cytomegalovirus disease

Initial therapy

The usual adult dosage is 900 mg of valganciclovir administered orally twice daily after meals.

Maintenance therapy

The usual adult dosage is 900 mg of valganciclovir administered orally once daily after a meal.

Prevention of cytomegalovirus disease in organ transplant recipients (excluding hematopoietic stem cell transplant recipients)

The usual adult dosage is 900 mg of valganciclovir administered orally once daily after a meal.

The usual pediatric dosage is the dose determined according to the equation shown below, administered orally once daily after a meal. The daily dose should not exceed 900 mg. If the patient's estimated glomerular filtration rate (eGFR) is >150, the eGFR value in the equation should be 150.

Dose (mg) = 7 × body surface area (m^2) × eGFR (mL/min/1.73 m^2)

~~Treatment of~~ Symptomatic congenital cytomegalovirus disease

The usual dosage for neonates and infants is 16 mg/kg of valganciclovir administered orally twice daily.

(The strikethrough denotes deletions from the proposed text.)

Approval Condition

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

Appendix

List of Abbreviations

ABR	Auditory brainstem response
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}th}$	Area under the concentration-time curve from time 0 to t hours post-dose
CLcr	Creatinine clearance
C_{max}	Maximum concentration
CMV	Cytomegalovirus
DNA	Deoxyribonucleic acid
DQ	Developmental quotient
FAS	Full analysis set
Foreign treatment guidelines	Treatment guidelines by the International Congenital Cytomegalovirus Recommendations Group and the European Society of Paediatric Infectious Diseases
G-CSF	Granulocyte colony stimulating factor
GCV	Ganciclovir
HIV	Human immunodeficiency virus
ITT	Intent-to-treat
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
Valganciclovir	Valganciclovir hydrochloride