Report on the Deliberation Results

March 3, 2016

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

[Brand name]	Proemend for Intravenous Infusion 150 mg
[Non-proprietary name]	Fosaprepitant Meglumine (JAN*)
[Applicant]	Ono Pharmaceutical Co., Ltd.
[Date of application]	May 27, 2015

[Results of deliberation]

In the meeting held on February 24, 2016, the First 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 re-examination period is 4 years.

[Conditions for approval] The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

February 4, 2016
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Proemend for Intravenous Infusion 150 mg
[Non-proprietary name]	Fosaprepitant Meglumine
[Applicant]	Ono Pharmaceutical Co., Ltd.
[Date of application]	May 27, 2015
[Dosage form/Strength]	Lyophilized powder in a vial to be reconstituted prior to infusion: Each vial contains 245.3 mg of fosaprepitant meglumine (150.0 mg of fosaprepitant)[1]
[Application classification]	Prescription drug (6) Drug with a new dosage
[Items warranting special mention]	None
[Previewing office]	Office of New Drug I

[1] The actual content is 257.6 mg of fosaprepitant meglumine (157.5 mg of fosaprepitant), overfilled by 5%.

Review Results

February 4, 2016

[Brand name] Proemend for Intravenous Infusion 150 mg
[Non-proprietary name] Fosaprepitant Meglumine
[Applicant] Ono Pharmaceutical Co., Ltd.
[Date of application] May 27, 2015
[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in treating pediatric patients is expected and its safety is acceptable in view of its observed benefits.

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

[Indication] Acute or delayed digestive symptoms (nausea and vomiting) resulting from the administration of antineoplastic agents such as cisplatin

[Dosage and administration]

- Adults and adolescents aged ≥12 years

  The usual dosage for adults and adolescents aged ≥12 years is 150 mg of fosaprepitant infused intravenously once on the first day of antineoplastic administration, in combination with other antiemetic agents.

- Infants aged ≥6 months and children aged <12 years

  The usual dosage for infants aged ≥6 months and children aged <12 years is 3.0 mg/kg of fosaprepitant infused intravenously once on the first day of antineoplastic administration, in combination with other antiemetic agents.

  A single dose of fosaprepitant should not exceed 150 mg.

(The underline denotes added text.)

[Conditions for approval] The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

December 9, 2015

I. Product Submitted for Registration

[Brand name]	Proemend for Intravenous Infusion 150 mg
[Non-proprietary name]	Fosaprepitant Meglumine
[Applicant]	Ono Pharmaceutical Co., Ltd.
[Date of application]	May 27, 2015
[Dosage form/Strength]	Lyophilized powder in a vial to be reconstituted prior to infusion: Each vial contains 245.3 mg of fosaprepitant meglumine (150.0 mg of fosaprepitant)[1]
[Indication]	Acute or delayed digestive symptoms (nausea and vomiting) resulting from the administration of antineoplastic agents such as cisplatin
[Dosage and administration]	• Adults and adolescents aged ≥12 years The usual dosage for adults and adolescents aged ≥12 years is 150 mg of fosaprepitant infused intravenously once on the first day of antineoplastic administration, in combination with other antiemetic agents. • Infants aged ≥6 months and children aged <12 years The usual dosage for infants aged ≥6 months and children aged <12 years is 3.0 mg/kg of fosaprepitant administered as an intravenous infusion once on the first day of antineoplastic administration, in combination with other antiemetic agents. A single dose of fosaprepitant should not exceed 150 mg, the usual dose for adults and adolescents aged ≥12 years. (The underline denotes added text.)

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

This application seeks the approval of new dosages, and therefore, the submitted data do not include pharmacological or pharmacokinetic study results in "Data relating to quality" or "Non-clinical data".

1. Origin or history of discovery, use in foreign countries, and other information

The administration of antineoplastic agents such as cisplatin (CDDP) causes chemotherapy-induced nausea and vomiting (CINV) resulting from the stimulation of the vomiting center due to an increased

[1] The actual content is 257.6 mg of fosaprepitant meglumine (157.5 mg of fosaprepitant), overfilled by 5%.

release of serotonin (5-hydroxytryptamine, 5-HT) from enterochromaffin cells located in the gastrointestinal mucosa. It has been reported[2] that the administration of antineoplastic agents also increases the release of substance P present in enterochromaffin cells, which binds to neurokinin (NK) 1 receptors in the central nervous system, thereby triggering CINV. CINV occurs in > 90% of patients receiving antineoplastic agents[3] such as CDDP and is a cause for discontinuing cancer chemotherapy. Thus, there is a need for appropriate antiemetic treatment.

Proemend for Intravenous Infusion 150 mg is an infusion containing fosaprepitant meglumine (hereinafter referred to as "fosaprepitant") as the active ingredient. Fosaprepitant is a phosphorylated prodrug of aprepitant, a non-peptide selective NK_1 receptor antagonist, with improved water solubility. After intravenous administration, fosaprepitant undergoes phosphatase-mediated rapid metabolic conversion to its active form, aprepitant. In September 2011, fosaprepitant was approved for adult use with the current dosage and administration and the following indication: acute or delayed digestive symptoms (nausea and vomiting) resulting from the administration of antineoplastic agents such as cisplatin.

Outside Japan, as of March 2015, fosaprepitant is approved in 75 countries, including the United States and Europe, for the indication of the prevention of nausea and vomiting associated with antineoplastic treatment.

In Japan, oral formulation of aprepitant (Emend Capsules 125 mg, 80 mg, and Emend Capsules Set) was approved for adult use in October 2009 for the following indication: acute or delayed digestive symptoms (nausea and vomiting) resulting from the administration of antineoplastic agents such as cisplatin, and in June 2012 for pediatric use in adolescents aged ≥12 years who can swallow capsules.

In Japan, ternary combinations of NK_1 receptor antagonists, $5\text{-}HT_3$ receptor antagonists, and corticosteroids are commonly used to control vomiting associated with antineoplastic treatment (Guidelines for Proper Use of Antiemetics [in Japanese], version 1.2, June 2014, Japan Society of Clinical Oncology). However, given the need for NK_1 receptor antagonists suitable for use in pediatric patients who have difficulty swallowing capsules, the applicant has developed fosaprepitant for pediatric use and filed the application.

2. Non-clinical data

The applicant has submitted no data of pharmacological or pharmacokinetic study results.

[2] *Drug Metab Dispos* 2003;31:785-791; *Neuropharmacology* 1996;35:1121-1129; *Neuropharmacology* 1993;32:799-806
[3] *Clin J Oncol Nurs* 2002;6:94-102; *N Engl J Med* 1993;329:1790-1796

2.(i) Summary of toxicology studies

2.(i).A Summary of the submitted data

The applicant submitted the toxicity data on Proemend for Intravenous Infusion 150 mg (fosaprepitant) at the initial application for approval (see "Review Report of Proemend for Intravenous Infusion 150 mg" [in Japanese only]; July 15, 2011). Since this application includes infants aged ≥6 months and children <12 years as a target population, the applicant submitted toxicity data obtained in juvenile dogs as the evaluation data. The dose is expressed in fosaprepitant equivalent.

Toxicology study in juvenile dogs (4.2.3.5.4-2: Study Identifier TT#[redacted]-9017)

Fosaprepitant was intravenously administered at 2, 4, and 6 mg/kg/day for 4 weeks to 14-day-old male and female beagles. In female beagles treated at ≥4 mg/kg/day, reduced body weight gain, increased uterus weight, thickening of intima and muscle layer from uterine horn to uterine corpus, thickening of cervical muscle layer, and edemas of vaginal lamina propria and submucosal layer were observed. In male beagles treated at 6 mg/kg/day, decreased testis weight and diminished Leydig cells in the testes were observed.[4] On the basis of these data, the no-observed-adverse-effect level (NOAEL) was judged to be 2 mg/kg/day in female beagles and 4 mg/kg/day in male beagles.

2.(i).B Outline of the review by PMDA

The effect of aprepitant on reproductive organs in adolescents was already evaluated in a toxicity study in juvenile dogs and a toxicity study in juvenile rats (see "Review Report of Emend Capsules 80 mg, 125 mg, Emend Capsules Set" [in Japanese only]; May 15, 2012). The applicant explained that the toxicity data in juvenile animals would be provided in the package insert of fosaprepitant, and PMDA considered there should be no special problems with the response by the applicant.

3. Clinical data

3.(i) Summary of biopharmaceutic studies and associated analytical methods

3.(i).A Summary of the submitted data

The applicant has submitted no new biopharmaceutic study data.

Plasma concentrations of fosaprepitant (unchanged form) and aprepitant (active form) were determined using the liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. The lower limit of quantification was 10 ng/mL for fosaprepitant and 1 ng/mL for aprepitant.

3.(ii) Summary of clinical pharmacology studies

3.(ii).A Summary of the submitted data

3.(ii).A.(1) Japanese pediatric study (5.3.5.2-1: Study Identifier ONO-7847-03, [redacted] 20[redacted] to [redacted] 20[redacted])

[See "3.(iii).A.(1) Japanese pediatric study" for the summary of the study.]

[4] Observed at Week 4

Fosaprepitant was intravenously administered at 3.0 mg/kg (up to 150 mg) to infants aged ≥6 months and children aged <12 years and 150 mg to adolescents aged ≥12 years and ≤18 years in Japanese pediatric patients with malignant tumors. The pharmacokinetic parameters of aprepitant are shown in Table 1.

Table 1. Pharmacokinetic parameters of aprepitant in Japanese pediatric patients

Dose	3.0 mg/kg (up to 150 mg)			150 mg
Age	≥6 months and <2 years	≥2 years and <6 years	≥6 years and <12 years	≥12 years and ≤18 years
Number of patients	5	5	5	11
AUC_{inf} (μg·h/mL)	17.6, 25.2 a)	29.3 ± 3.3 b)	45.5 ± 16.1	61.1 ± 29.2
C_{24h} (ng/mL)	116 ± 51	201 ± 92	542 ± 407	989 ± 774
C_{48h} (ng/mL)	2.66 ± 0.92	7.63 ± 11.2	41.9 ± 50.8	204 ± 198
C_{72h} (ng/mL)	0.00, 0.00 a)	0.58 ± 1.16 b)	5.53 ± 6.13	60.5 ± 82.7
$t_{1/2}$ (h)	4.40, 4.42 a)	5.15 ± 1.55 b)	6.63 ± 0.94	10.1 ± 4.2

Mean ± standard deviation (SD)
a) n = 2, individual values calculated from measured values at time points at which blood was collected
b) n = 4

3.(ii).B Outline of the review by PMDA

The applicant's explanation on the pharmacokinetics of fosaprepitant in pediatric patients:
A dose of 3.0 mg/kg was selected for infants aged ≥6 months and children aged <12 years in the Japanese pediatric study (ONO-7847-03) because it was an estimated dose for achieving an aprepitant exposure equivalent to that after intravenous administration of fosaprepitant at 150 mg to adults. The plasma concentrations of aprepitant after intravenous administration of fosaprepitant at 3.0 mg/kg to Japanese infants aged ≥6 months and children aged <12 years shown in Table 1 tended to remain lower than those after intravenous administration of 150 mg to healthy Japanese adults shown in Table 2.

In the Japanese pediatric study (ONO-7847-03), the dosage and administration approved for adults were selected for adolescent patients aged ≥12 years and ≤18 years. As shown in Table 2, AUC_{inf} and C_{24h} in Japanese adolescent patients aged ≥12 years and ≤18 years were comparable to those in healthy adults. Although C_{48h} and C_{72h} tended to be lower in adolescent patients, given the fact that there was the effect of inter-individual differences, the ranges of distribution of plasma concentrations were generally overlapping.

The adolescents tended to show a faster elimination of aprepitant than healthy adults; this was probably partly because younger adolescents have a higher clearance of liver-metabolized aprepitant due to large liver volume per body weight.

Table 2. Pharmacokinetic parameters of aprepitant after administration of fosaprepitant in Japanese adolescent patients aged ≥12 years and ≤18 years and healthy adults

	Adolescent (≥12 years and ≤18 years) (n = 11)	Adult (n = 24)	Geometric mean ratio (adolescent/adult) [90% confidence interval]
AUC_{inf} (μg·h/mL)	61.1 ± 29.2	54.8 ± 16.6	1.03 [0.83–1.29]
C_{24h} (ng/mL)	989 ± 774	977 ± 315	0.81 [0.60–1.09]
C_{48h} (ng/mL)	204 ± 198	363 ± 188	0.31 [0.17–0.54]
C_{72h} (ng/mL)	60.5 ± 82.7	110 ± 95	0.23 [0.11–0.49]

Mean ± SD

PMDA's view:

Since exposure to fosaprepitant did not tend to increase in pediatric patients compared to healthy adults, there are no specific pharmacokinetic concerns over administration of fosaprepitant to pediatric patients at this point. However, since changes in blood concentrations over time showed a tendency for faster elimination in pediatric patients compared to adults, the effect on efficacy is discussed further in the clinical section [see "3.(iii).B.(1) Efficacy" and "3.(iii).B.(4) Dosage and administration"].

3.(iii) Summary of clinical efficacy and safety

3.(iii).A Summary of the submitted data

The applicant submitted the results of the Japanese pediatric study (ONO-7847-03) as evaluation data.

3.(iii).A.(1) Japanese pediatric study (5.3.5.2-1: Study Identifier ONO-7847-03, [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted at 8 study sites in Japan to evaluate the safety and efficacy of fosaprepitant in preventing CINV and its pharmacokinetics in patients with malignant tumors aged ≥6 months and ≤18 years scheduled to receive chemotherapy[5] (target sample size, 24 patients in total: ≥6 months and <2 years, 5; ≥2 years and <6 years, 5; ≥6 years and <12 years, 5; ≥12 years and ≤18 years, 9).

The dosage regimens are shown in Table 3. On Day 1, fosaprepitant was intravenously administered as a single dose, starting 1 hour (patients aged ≥12 years and ≤18 years) or 1.5 hours (patients aged ≥6 months and <12 years) before the first administration of antineoplastic agents that were moderately or highly emetogenic.[6] On Day 1, dexamethasone (DEX)[7] was intravenously administered for ≤30 minutes, starting 30 minutes before the first administration of antineoplastic agents that were moderately or highly emetogenic. On Days 2 and 3, DEX was administered intravenously in the morning. On Day 1, granisetron hydrochloride (GRN) was intravenously administered for ≤30 minutes, starting 30 minutes before the first administration of antineoplastic agents that were moderately or highly emetogenic. Between Days 2 and 5, patients were allowed to receive intravenous GRN only on the days when they received cisplatin (CDDP), cyclophosphamide (CPA), carboplatin (CBDCA), or a moderately or highly emetogenic antineoplastic agents. The follow-up period was 15 days.

Table 3. Dosage regimens

	≥6 months and <12 years	≥12 years and ≤18 years
Fosaprepitant	**Day 1: 3.0 mg/kg (up to 150 mg) administered over 60 minutes**	**Day 1: 150 mg administered over 30 minutes**
DEX	**Days 1 and 2: 0.1 mg/kg (up to 4 mg) Day 3: 0.2 mg/kg (up to 8 mg)**	**Days 1 and 2: 4 mg Day 3: 8 mg**
GRN	**Day 1: 40 μg/kg (between Days 2 and 5: 40 μg/kg)***	

The study drug was intravenously administrated in all treatment groups.

*, Prophylactic administration was permitted only on the days when CDDP, CPA, CBDCA, or moderately or highly emetogenic antineoplastic agent was to be administered.

[5] Chemotherapy with cisplatin (CDDP), cyclophosphamide (CPA), or carboplatin (CBDCA)

[6] Antineoplastic agents classified as "highly emetogenic" or "moderately emetogenic" by the American Society of Clinical Oncology (ASCO) Practice Guideline Update 2011 (*J Clin Oncol* 2011;29:4189-4198)

[7] Dexamethasone phosphate was used in the study.

A total of 27 subjects (≥6 months and <2 years, 5; ≥2 years and <6 years, 5; ≥6 years and <12 years, 5; ≥12 years and ≤18 years, 12) received the study drug. All of them were included in the full analysis set (FAS) and safety set (SAF), and analyzed for efficacy, safety, and pharmacokinetics. There were no treatment discontinuations.

Adverse events occurred in all subjects. Adverse events reported in ≥10% of all subjects are shown in Table 4. Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) were reported in 14.8% (4 of 27 subjects: abdominal pain upper and headache, glucose urine present, lymphocyte count decreased, and hiccups, each in 1 subject).

Table 4. Adverse events reported in ≥10% of subjects

	≥6 months and <2 years (n = 5)	≥2 years and <6 years (n = 5)	≥6 years and <12 years (n = 5)	≥12 years and ≤18 years (n = 12)	Overall (n = 27)
Any adverse event	**100.0% (5)**	**100.0% (5)**	**100.0% (5)**	**100.0% (12)**	**100.0% (27)**
Lymphocyte count decreased	**100.0% (5)**	**100.0% (5)**	**100.0% (5)**	**91.7% (11)**	**96.3% (26)**
Neutrophil count decreased	**100.0% (5)**	**100.0% (5)**	**100.0% (5)**	**83.3% (10)**	**92.6% (25)**
White blood cell count decreased	**100.0% (5)**	**100.0% (5)**	**100.0% (5)**	**83.3% (10)**	**92.6% (25)**
Anaemia	**80.0% (4)**	**100.0% (5)**	**80.0% (4)**	**41.7% (5)**	**66.7% (18)**
Platelet count decreased	**40.0% (2)**	**80.0% (4)**	**80.0% (4)**	**50.0% (6)**	**59.3% (16)**
Malaise	**40.0% (2)**	**40.0% (2)**	**100.0% (5)**	**33.3% (4)**	**48.1% (13)**
Decreased appetite	**40.0% (2)**	**20.0% (1)**	**60.0% (3)**	**41.7% (5)**	**40.7% (11)**
Vomiting	**20.0% (1)**	**40.0% (2)**	**40.0% (2)**	**33.3% (4)**	**33.3% (9)**
Haematocrit decreased	**60.0% (3)**	**80.0% (4)**	**20.0% (1)**	**0.0% (0)**	**29.6% (8)**
Red blood cell count decreased	**60.0% (3)**	**80.0% (4)**	**20.0% (1)**	**0.0% (0)**	**29.6% (8)**
Febrile neutropenia	**20.0% (1)**	**40.0% (2)**	**40.0% (2)**	**16.7% (2)**	**25.9% (7)**
Nausea	**0.0% (0)**	**20.0% (1)**	**20.0% (1)**	**41.7% (5)**	**25.9% (7)**
ALT increased	**0.0% (0)**	**60.0% (3)**	**20.0% (1)**	**16.7% (2)**	**22.2% (6)**
Headache	**0.0% (0)**	**0.0% (0)**	**60.0% (3)**	**25.0% (3)**	**22.2% (6)**
Constipation	**20.0% (1)**	**40.0% (2)**	**0.0% (0)**	**16.7% (2)**	**18.5% (5)**
Stomatitis	**0.0% (0)**	**0.0% (0)**	**80.0% (4)**	**8.3% (1)**	**18.5% (5)**
Hyponatraemia	**0.0% (0)**	**0.0% (0)**	**20.0% (1)**	**33.3% (4)**	**18.5% (5)**
AST increased	**0.0% (0)**	**40.0% (2)**	**20.0% (1)**	**8.3% (1)**	**14.8% (4)**
Weight decreased	**20.0% (1)**	**20.0% (1)**	**40.0% (2)**	**0.0% (0)**	**14.8% (4)**
Insomnia	**0.0% (0)**	**0.0% (0)**	**0.0% (0)**	**25.0% (3)**	**11.1% (3)**

MedDRA/J ver. 17.0
Proportion % (number of subjects)

No deaths occurred. The incidence of serious adverse events was 7.4% (2 of 27 subjects: febrile neutropenia; 1 subject each in 1-year-old and 9-year-old subjects). A causal relationship with the study drug was ruled out for both events, and their outcomes were recovered/resolved.

The proportion of subjects who achieved "Complete Response (no vomiting and no use of rescue therapy, CR)" at 0 to 120 hours[8] (overall phase) was 40.7% (11 of 27 subjects). The proportion of subjects with "no vomiting" or "no use of rescue therapy" is shown in Table 5.

[8] The initiation of administration of moderately or highly emetogenic antineoplastic agent on Day 1 is defined as 0 hours.

Table 5. Major results regarding efficacy

Dose		3 mg/kg				150 mg	Overall (n = 27)
Age		Total of ≥6 months and <12 years (n = 15)	≥6 months and <2 years (n = 5)	≥2 years and <6 years (n = 5)	≥6 years and <12 years (n = 5)	≥12 years and ≤18 years (n = 12)	
CR	Overall	53.3% (8)	80.0% (4)	40.0% (2)	40.0% (2)	25.0% (3)	40.7% (11)
	Acute	86.7% (13)	80.0% (4)	80.0% (4)	100.0% (5)	75.0% (9)	81.5% (22)
	Delayed	60.0% (9)	100.0% (5)	40.0% (2)	40.0% (2)	25.0% (3)	44.4% (12)
No vomiting	Overall	53.3% (8)	80.0% (4)	40.0% (2)	40.0% (2)	25.0% (3)	40.7% (11)
	Acute	86.7% (13)	80.0% (4)	80.0% (4)	100.0% (5)	75.0% (9)	81.5% (22)
	Delayed	60.0% (9)	100.0% (5)	40.0% (2)	40.0% (2)	25.0% (3)	44.4% (12)
No use of rescue therapy	Overall	80.0% (12)	100.0% (5)	80.0% (4)	60.0% (3)	58.3% (7)	70.4% (19)
	Acute	100.0% (15)	100.0% (5)	100.0% (5)	100.0% (5)	91.7% (11)	96.3% (26)
	Delayed	80.0% (12)	100.0% (5)	80.0% (4)	60.0% (3)	58.3% (7)	70.4% (19)

The initiation of administration of moderately or highly emetogenic antineoplastic agent on Day 1 is defined as 0 hour.
Overall phase, 0 to 120 hours; acute phase, 0 to 24 hours; delayed phase, >24 to 120 hours
Proportion % (number of subjects)

For the pharmacokinetics, see "3.(ii).A.(1) Japanese pediatric study."

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Efficacy

In the Japanese pediatric study (ONO-7847-03), the dose per body weight was determined for pediatric subjects aged ≥6 months and <12 years and the approved adult dose (150 mg) was used for pediatric subjects aged ≥12 years and ≤18 years. Therefore, the efficacy of fosaprepitant was evaluated separately in two age groups: ≥6 months and <12 years; and ≥12 years and ≤18 years. As a result, PMDA determined that fosaprepitant is expected to be effective in pediatric patients aged ≥12 years and ≤18 years and those aged ≥6 months and <12 years. However, information regarding the efficacy of fosaprepitant in routine pediatric use needs to be collected by post-marketing surveillance because the Japanese pediatric study (ONO-7847-03) evaluated only a limited number of subjects.

The efficacy of fosaprepitant will be finalized, taking into account the comments made in the Expert Discussion.

3.(iii).B.(1).1) Efficacy in infants aged ≥6 months and children aged <12 years

The applicant's explanation of the efficacy of fosaprepitant in infants aged ≥6 months and children aged <12 years:

The Japanese pediatric study (ONO-7847-03) was designed as an open-label, uncontrolled study, and no standard treatment group was included due to the following reasons: (1) the potential difficulties in obtaining consent from pediatric patients with malignant tumors or from their parent(s)/legal guardian for a standard-treatment-controlled, comparative study even if all the patients to be included were eligible for the standard treatment; (2) there existed foreign pediatric studies which included a group receiving the standard treatment alone. The efficacy of fosaprepitant was then evaluated by reference to the data from the standard treatment groups of the foreign pediatric studies.

In the Japanese pediatric study (ONO-7847-03), the overall phase CR rate in subjects aged ≥6 months and <12 years was 53.3% (8 of 15 subjects) (Table 5).

Outside Japan, Studies P134[9] (reference data) and P208[10] (reference data) were conducted as clinical studies in which a group of pediatric patients aged ≥6 months and <12 years treated with the standard treatment alone (standard treatment group) were included. In Study P134, the overall phase CR rate in the standard treatment group was 10.5% (2 of 19 subjects), and by age group as follows: 16.7% (1 of 6 subjects) of subjects aged ≥6 months and <2 years; 16.7% (1 of 6 subjects) of subjects aged ≥2 years and <6 years; and 0.0% (0 of 7 subjects) of subjects aged ≥6 years and <12 years. In Study P208, the overall phase CR rate in the standard treatment group was 25.5% (26 of 102 subjects), and by age group as follows: 25.0% (4 of 16 subjects) of subjects aged ≥6 months and <2 years; 30.2% (13 of 43 subjects) of subjects aged ≥2 years and <6 years; and 20.9% (9 of 43 subjects) of subjects aged ≥6 years and <12 years. The overall phase CR rate in the Japanese pediatric study (ONO-7847-03) was higher than those in the standard treatment groups of Studies P134 and P208, and therefore fosaprepitant is expected to be effective in pediatric patients aged ≥6 months and <12 years.

In the Japanese pediatric study (ONO-7847-03), the overall phase CR rate was evaluated by age group in subjects aged ≥6 months and <12 years. The overall phase CR rate in subjects aged ≥2 years and <6 years and subjects aged ≥6 years and <12 years (both 40.0%, 2 of 5 subjects) were lower than that in subjects aged ≥6 months and <2 years (80.0%, 4 of 5 subjects) (Table 5). An investigation of the reasons suggested that it was attributable to the dose of emetogenic antineoplastic agent. The mean dose of CDDP in subjects treated with regimens including highly emetogenic CDDP was 62.0 mg/m^2 in subjects aged ≥6 months and <2 years, 103.3 mg/m^2 in subjects aged ≥2 years and <6 years, and 97.6 mg/m^2 in subjects aged ≥6 years and <12 years. The mean dose of CDDP tended to be higher in subjects aged ≥2 years and <6 years and in those aged ≥6 years and <12 years, and thus a potential effect of the CDDP dose was considered. The CR rate tended to be low in subjects who concomitantly received a moderately or highly emetogenic Actinomycin D[11] among subjects treated with regimens including moderately to highly emetogenic CPA[12] (CPA regimen)[13]; therefore, the CPA dose in subjects who were given Actinomycin D in the CPA regimen was evaluated. The CPA doses in 3 subjects aged ≥2 years and <6 years or ≥6 years and <12 years were 1687 mg/m^2, 2158 mg/m^2, and 2186 mg/m^2, and none of the 3 subjects achieved CR.[14] On the other hand, the CPA doses in 2 subjects aged ≥6 months and <2 years were 1645 mg/m^2 and 1660 mg/m^2, and both subjects achieved CR. These results showed a possible effect of CPA dose.

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9 Ondansetron was intravenously administered before 3-day treatment with antineoplastic agents between Days 1 and 3 (standard treatment group) to 19 pediatric patients with malignant tumors aged ≥6 months and <12 years in an open-label, uncontrolled manner. The study also included a treatment group in which an intravenous dose of ondansetron and an intravenous dose of fosaprepitant equivalent to 150 mg for patients aged ≥12 years were administered over ≥60 minutes, on Day 1 only in an open-label, uncontrolled manner, approximately 105 minutes before administration of antineoplastic agents to 22 pediatric patients with malignant tumor aged ≥6 months and <12 years.

10 A double-blind comparative study to evaluate the efficacy and safety of add-on therapy of oral aprepitant to intravenous ondansetron compared with the standard treatment in pediatric patients with malignant tumors aged ≥6 months and ≤17 years. Administration of dexamethasone was accepted at the discretion of the physician.

11 Actinomycin D is categorized as highly emetogenic in the ASCO guideline Updated 2011 (*J Clin Oncol* 2011;29:4189-4198) and moderately emetogenic in the NCCN Clinical Practice Guidelines in Oncology "Antiemesis" 2014.

12 Cyclophosphamide is categorized as highly emetogenic at ≥1500 mg/m^2 and moderately emetogenic at <1500 mg/m^2 in the ASCO guideline Update 2011 (*J Clin Oncol* 2011;29:4189-4198).

13 Subjects who received both CPA and CDDP were handled as those who received CDDP, more highly emetogenic than CPA, and not included in the concerned subjects.

14 The subject to whom 1687 mg/m^2 was administered achieved CR from 0 to 96 hours.

PMDA's view:

The comparison between the Japanese pediatric study (ONO-7847-03) and the foreign pediatric studies has limitations in that the Japanese pediatric study (ONO-7847-03) evaluated only a limited number of pediatric subjects aged ≥6 months and <12 years, and that the standard treatment groups of the foreign pediatric studies were external controls. However, the overall phase CR rate for each age group tended to be higher in the Japanese pediatric study (ONO-7847-03) than in the standard treatment groups of the foreign pediatric studies, and fosaprepitant is listed[15] as a standard treatment for adult patients to prevent CINV associated with administration of agents such as CDDP; therefore, fosaprepitant is expected to be effective in pediatric patients aged ≥6 months and <12 years.

3.(iii).B.(1).2) Efficacy in adolescents aged ≥12 years and ≤18 years

The applicant's explanation of the efficacy in adolescents aged ≥12 years and ≤18 years:

Aprepitant capsules are approved for use in adolescent patients aged ≥12 years and ≤18 years in Japan. The overall phase CR rate (25.0%, 3 of 12 subjects) in adolescent subjects aged ≥12 years and ≤18 years in the Japanese pediatric study (ONO-7847-03) was lower than that (45.5%, 10 of 22 subjects) in the Japanese pediatric study of aprepitant capsules (pediatric subjects aged ≥12 years and ≤18 years in ONO-7436-03) (see "Review Report of Emend Capsules 125 mg, etc."; May 15, 2012 [in Japanese only]) (Table 6). The reasons for this difference were investigated in the context of the pharmacokinetics and the antineoplastic agents administered.

Fosaprepitant is infused intravenously and plasma aprepitant concentrations at 48 hours postdose tended to be lower than those after aprepitant capsules are administered (plasma aprepitant concentrations at 24 hours postdose, 989 ± 774 ng/mL for fosaprepitant, 675 ± 482 ng/mL for aprepitant capsules; those at 48 hours postdose, 204 ± 198 ng/mL for fosaprepitant, 492 ± 408 ng/mL for aprepitant capsules). In the Japanese pediatric study (ONO-7847-03), time to vomiting or rescue therapy was generally within 30 hours after initiation of administration of moderately or highly emetogenic antineoplastic agent, during which period the plasma aprepitant concentrations after administration of fosaprepitant were comparable to those after administration of aprepitant capsules. These results suggested that the differences in the changes in plasma aprepitant concentrations between fosaprepitant and aprepitant capsules were unlikely to have an effect on the efficacy.

[15] Guidelines for Proper Use of Antiemetics [in Japanese], version 1.2, June 2014, Japan Society of Clinical Oncology

Table 6. Efficacy of fosaprepitant and aprepitant capsules in the Japanese pediatric study (≥12 years and ≤18 years)

		Fosaprepitant Japanese pediatric study (ONO-7847-03) n = 12	Aprepitant capsules Japanese pediatric study (ONO-7436-03) n = 22
CR	Overall	25.0% (3)	45.5% (10)
	Acute	75.0% (9)	68.2% (15)
	Delayed	25.0% (3)	59.1% (13)
No vomiting	Overall	25.0% (3)	63.6% (14)
	Acute	75.0% (9)	72.7% (16)
	Delayed	25.0% (3)	72.7% (16)
No use of rescue therapy	Overall	58.3% (7)	59.1% (13)
	Acute	91.7% (11)	81.8% (18)
	Delayed	58.3% (7)	72.7% (16)

The initiation of administration of moderately or highly emetogenic antineoplastic agent on Day 1 is defined as 0 hours.
Overall phase, 0 to 120 hours; acute phase, 0 to 24 hours; delayed phase, >24 to 120 hours.
Proportion % (number of subjects).

Subsequently, the type and dose of antineoplastic agents administered were investigated. The dose of each major antineoplastic agent (CDDP, CPA, and CBDCA) and the overall phase CR rate are shown in Table 7. There was no marked difference in the CDDP dose. No comparison was possible for CBDCA because no subjects were treated with CBDCA in the Japanese pediatric study (ONO-7847-03). In the subjects treated with CPA, the Japanese pediatric study (ONO-7847-03) showed a higher mean dose and a lower overall phase CR rate than the Japanese pediatric study of aprepitant capsules (ONO-7436-03) showed. In the Japanese pediatric study (ONO-7847-03), an extremely high dose of CPA (4107 mg/m^2) was administered to 1 subject. Even if this subject was excluded, the overall phase CR rate was still as low as 20.0% (1 of 5 subjects) in subjects treated with CPA in the Japanese pediatric study (ONO-7847-03). Therefore, the degree of emetogenicity of antineoplastic agents coadministered was further determined (Table 8).

Table 7. Overall phase CR by major antineoplastic agents (≥12 years and ≤18 years)

		Fosaprepitant Japanese pediatric study (ONO-7847-03) n = 12	Aprepitant capsules Japanese pediatric study (ONO-7436-03) n = 22
CDDP	Mean dose ± SD (mg/m^2)	101.6 ± 9.1	106.0 ± 11.2
	Min to max (mg/m^2)	96.2 to 119.9	92.6 to 120.0
	CR rate (n)	33.3% (2/6)	20.0% (2/10)
CPA	Mean dose ± SD (mg/m^2)	1884 ± 1157	1537 ± 445
	Min to max (mg/m^2)	1145 to 4107	1165 to 2260
	CR rate (n)	16.7% (1/6)	75.0% (6/8)
CBDCA	Mean dose ± SD (mg/m^2)	Not applicable	408.4 ± 23.0
	Min to max (mg/m^2)		392.0 to 442.5
	CR rate (n)		50.0% (2/4)

Dose, total dose administered between Days 1 and 6.

Table 8. CR by emetogenicity of antineoplastic agents coadministered to subjects treated with CPA (≥12 years and ≤18 years)

Major antineoplastic agents	Emetogenicity of antineopolastic agents coadministered	Fosaprepitant Japanese pediatric study (ONO-7847-03) n = 6	Aprepitant capsules Japanese pediatric study (ONO-7436-03) n = 8
CPA	Minimally emetogenic	Not applicable	100.0% (1/1)
	Low emetogenic	Not applicable	100.0% (2/2)
	Moderately emetogenic	25.0% (1/4)	100.0% (2/2)
	Highly emetogenic	0.0% (0/2)	33.3% (1/3)

The antineoplastic agents used in combination were categorized by the most emetogenic agent in the combination according to the ASCO guideline (2011).

Of the subjects treated with CPA, all subjects in the Japanese pediatric study (ONO-7847-03) received moderately or highly emetogenic antineoplastic agents, while 37.5% (3 of 8) of subjects in the Japanese pediatric study of aprepitant capsules (ONO-7436-03) received minimally or mildly emetogenic antineoplastic agents. This suggested that the differences in the emetogenicity of the coadministered antineoplastic agents affected the overall phase CR rate. In subjects treated with CBDCA, the overall phase CR rate was 50.0% (2 of 4 subjects) in the Japanese pediatric study of aprepitant capsules (ONO-7436-03) and no subjects were treated with CBDCA in the Japanese pediatric study (ONO-7847-03); this also indicated the effect of the difference on the overall phase CR rate. On the basis of the above results, the differences in the type and dose of antineoplastic agents administered were considered to be the possible cause of the lower overall phase CR rate in the Japanese pediatric study (ONO-7847-03) than in the Japanese pediatric study of aprepitant capsules (ONO-7436-03).

Outside Japan, Studies P208 and P097[16] (reference data) were conducted with the standard treatment group[17] in pediatric subjects aged ≥12 years and ≤18 years. The overall phase CR rate in the standard treatment group was 8.3% (4 of 48 subjects) in Study P208 and 5.6% (1 of 18 subjects) in Study P097. The overall phase CR rate in pediatric subjects aged ≥12 years and ≤18 years in the Japanese pediatric study (ONO-7847-03) was 25.0% (3 of 12 subjects), which was higher than that in the standard treatment groups of the foreign studies.

In a Japanese phase III study in adults (ONO-7847-01) (see "Review Report of Proemend for Intravenous Infusion 150 mg"; July 15, 2011), the overall phase CR rate following administration of the standard treatment and fosaprepitant 150 mg was 47.3% and 64.2% in the respective groups, demonstrating the superiority of the fosaprepitant group. Pediatric patients have been shown to have a high sensitivity to antineoplastic agents,[18] and more robust chemotherapy (higher dose of antineoplastic agent per body surface area) is performed in many cases compared to adult patients despite the risk for adverse reactions associated with antineoplastic agents; this may have affected the overall phase CR rate, and the overall phase CR rate was lower in the Japanese pediatric study (ONO-7847-03) than in the fosaprepitant group of the Japanese phase III study in adults (ONO-7847-01). The difference in the overall phase CR rate between the standard treatment group and the fosaprepitant group was 16.9% in the Japanese phase III study in adults (ONO-7847-01); the differences between the standard treatment groups in the foreign pediatric studies (P208 and P097) and the fosaprepitant group in the Japanese pediatric study (ONO-7847-03) were 16.7% (Study P208) and 19.4% (Study P097), which were consistent with that in the Japanese phase III study in adults (ONO-7847-01). The pharmacokinetics were generally similar between adult subjects and pediatric subjects aged ≥12 years and ≤18 years [see "3.(ii).B Outline of the review by PMDA"]. In summary, fosaprepitant is expected to be as effective in pediatric patients aged ≥12 years and ≤18 years as in the approved treatment in adult patients, in terms of superiority over the standard treatment.

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16 A double-blind comparative study to evaluate the efficacy and safety of add-on therapy of oral aprepitant capsules to intravenous ondansetron and oral dexamethasone compared with the standard treatment in pediatric patients with malignant tumors aged ≥12 years and ≤17 years.

17 Dexamethasone and ondansetron.

18 *Cancer* 2007;110:703-713, *Current Opinion in Chemical Biology* 2007;11:424-432

PMDA's view:

The applicant's explanation regarding the possible effects of differences in the type of antineoplastic agents on the overall phase CR rate in the Japanese pediatric study (ONO-7847-03) is understandable, though assessment has limitations because the Japanese pediatric study (ONO-7847-03) evaluated only a limited number of subjects. The comparison between the Japanese pediatric study (ONO-7847-03) and the foreign pediatric studies also has limitations because the standard treatment groups in the foreign pediatric studies were external controls. However, fosaprepitant is expected to be effective in pediatric patients aged ≥12 years and ≤18 years on the following grounds: (1) the overall phase CR rate in the standard treatment groups of the foreign pediatric studies was <10%; (2) the overall phase CR rate in the Japanese pediatric study (ONO-7847-03) tended to be higher than that in the standard treatment groups of the foreign studies; and (3) fosaprepitant is positioned as a standard treatment to prevent CINV associated with administration of agents such as CDDP in adults.

3.(iii).B.(2) Safety

PMDA considers that the safety of fosaprepitant in pediatric patients aged ≥6 months and <12 years and those aged ≥12 years and ≤18 years is acceptable on the basis of the applicant's explanations 1) to 4) below. However, information on the safety of the product in routine pediatric use needs to be collected by post-marketing surveillance, because the Japanese pediatric study (ONO-7847-03) evaluated only a limited number of subjects.

The safety of fosaprepitant will be finalized, taking into account the comments made in the Expert Discussion.

3.(iii).B.(2).1) Comparison of Study ONO-7847-03 and the Japanese pediatric study of aprepitant capsules

The applicant compared the incidence of adverse events in subjects aged ≥12 years and ≤18 years in the Japanese pediatric study (ONO-7847-03) with that in the Japanese pediatric study of aprepitant capsules (ONO-7436-03) (Table 9), and explained the safety of fosaprepitant as follows.

Table 9. Incidence of adverse events reported in ≥10% of the subjects in either study

	Fosaprepitant Japanese pediatric study (ONO-7847-03)	Aprepitant capsules Japanese pediatric study (ONO-7436-03)
	≥12 years and ≤18 years (n = 12)	≥12 years and ≤18 years (n = 22)
Any adverse event	100.0% (12)	100.0% (22)
Serious adverse events	0.0% (0)	9.1% (2)
Lymphocyte count decreased	91.7% (11)	81.8% (18)
Neutrophil count decreased	83.3% (10)	95.5% (21)
White blood cell count decreased	83.3% (10)	90.9% (20)
Platelet count decreased	50.0% (6)	81.8% (18)
Anaemia	41.7% (5)	18.2% (4)
Decreased appetite	41.7% (5)	50.0% (11)
Nausea	41.7% (5)	45.5% (10)
Malaise	33.3% (4)	50.0% (11)
Vomiting	33.3% (4)	22.7% (5)
Hyponatraemia	33.3% (4)	0.0% (0)
Headache	25.0% (3)	13.6% (3)
Insomnia	25.0% (3)	0.0% (0)
Febrile neutropenia	16.7% (2)	9.1% (2)
ALT increased	16.7% (2)	9.1% (2)
Constipation	16.7% (2)	18.2% (4)
Blood bilirubin increased	16.7% (2)	4.5% (1)
Hypokalaemia	16.7% (2)	0.0% (0)
Myositis	16.7% (2)	4.5% (1)
Paraesthesia	16.7% (2)	0.0% (0)
Hiccups	16.7% (2)	18.2% (4)
Stomatitis	8.3% (1)	13.6% (3)
AST increased	8.3% (1)	13.6% (3)
Pyrexia	8.3% (1)	13.6% (3)
Gamma-glutamyltransferase increased	8.3% (1)	18.2% (4)
Haematocrit decreased	0.0% (0)	50.0% (11)
Red blood cell count decreased	0.0% (0)	54.5% (12)
Blood sodium decreased	0.0% (0)	22.7% (5)
Haemoglobin decreased	0.0% (0)	59.1% (13)
Blood urea increased	0.0% (0)	13.6% (3)

MedDRA/J ver. 17.0
Proportion % (number of subjects)
* No deaths, adverse events that led to treatment discontinuation, or serious adverse drug reactions were reported in either age group.

The incidence of anaemia and hyponatraemia in pediatric subjects aged ≥12 years and ≤18 years tended to be higher in the Japanese pediatric study (ONO-7847-03) than in the Japanese pediatric study of aprepitant capsules (ONO-7436-03), and the underlying cause of this difference was investigated.

The difference in incidence of anaemia was due to the different versions of the CTCAE[19] used for the assessment of the severity of adverse events that were reported on case report forms in the Japanese pediatric study (ONO-7847-03) and Japanese pediatric study of aprepitant capsules (ONO-7436-03). In the Japanese pediatric study (ONO-7847-03), anaemia was reported in many subjects because it was listed in the CTCAE as an adverse event. In the Japanese pediatric study of aprepitant capsules (ONO-7436-03), anaemia was not listed in the CTCAE as an adverse event. Therefore, adverse events of anaemia, in some cases, could have been reported not as such but only as abnormal laboratory values (red blood cell count decreased, haematocrit decreased, haemoglobin decreased). However, there was no significant difference in the incidence between anaemia (41.7%) in the Japanese pediatric study (ONO-7847-03) and red blood cell count decreased (54.5%), haematocrit decreased (50.0%), or haemoglobin decreased (59.1%) in the Japanese pediatric study of aprepitant capsules (ONO-7436-03),

[19] Common Terminology Criteria for Adverse Events

and therefore it was concluded that there was no significant difference in the safety profiles of anaemia and the laboratory values suggestive of anaemia between these 2 studies.

Hyponatraemia was not reported in the Japanese pediatric study of aprepitant capsules (ONO-7436-03), but was reported in 33.3% (4 of 12 subjects) of subjects in the Japanese pediatric study (ONO-7847-03). Meanwhile, blood sodium decreased was reported in 22.7% (5 of 22 subjects) of subjects in the Japanese pediatric study of aprepitant capsules (ONO-7436-03). Therefore, there was no clinically significant difference in terms of reduced blood sodium level between the 2 studies.

The Japanese phase III study in adults (ONO-7847-01) and foreign pediatric studies (Studies P208 and P097) were the studies of fosaprepitant that included the standard treatment group, and there was no significant difference in the incidence of adverse events that were suggestive of cytopenia or hyponatraemia between the standard treatment group and the fosaprepitant group in any of these studies.

3.(iii).B.(2).2) Comparison by age group (≥6 months and <12 years versus ≥12 years and ≤18 years) in the Japanese pediatric study (ONO-7847-03)

The applicant explained the comparison of the incidence of adverse events between subjects aged ≥6 months and <12 years and those aged ≥12 years and ≤18 years in the Japanese pediatric study (ONO-7847-03) as follows.

There were no significant differences in the incidence of adverse events between subjects aged ≥6 months and <2 years, ≥2 years and <6 years, and ≥6 years and <12 years (Table 4); therefore, subjects aged ≥6 months and <12 years were pooled into one age group and compared with those aged ≥12 years and ≤18 years (Table 10).

Table 10. Incidence of adverse events reported in ≥10% of the subjects in either age group

	Japanese pediatric study (ONO-7847-03)	
	≥6 months and <12 years (n = 15)	≥12 years and ≤18 years (n = 12)
Any adverse event	100.0% (15)	100.0% (12)
Serious adverse events	13.3% (2)	0.0% (0)
Lymphocyte count decreased	100.0% (15)	91.7% (11)
Neutrophil count decreased	100.0% (15)	83.3% (10)
White blood cell count decreased	100.0% (15)	83.3% (10)
Anaemia	86.7% (13)	41.7% (5)
Platelet count decreased	66.7% (10)	50.0% (6)
Malaise	60.0% (9)	33.3% (4)
Haematocrit decreased	53.3% (8)	0.0% (0)
Red blood cell count decreased	53.3% (8)	0.0% (0)
Decreased appetite	40.0% (6)	41.7% (5)
Vomiting	33.3% (5)	33.3% (4)
Febrile neutropenia	33.3% (5)	16.7% (2)
ALT increased	26.7% (4)	16.7% (2)
Stomatitis	26.7% (4)	8.3% (1)
Weight decreased	26.7% (4)	0.0% (0)
Headache	20.0% (3)	25.0% (3)
Constipation	20.0% (3)	16.7% (2)
AST increased	20.0% (3)	8.3% (1)
Nausea	13.3% (2)	41.7% (5)
Urine ketone body present	13.3% (2)	0.0% (0)
Diarrhoea	13.3% (2)	0.0% (0)
Epistaxis	13.3% (2)	0.0% (0)
Hyponatraemia	6.7% (1)	33.3% (4)
Insomnia	0.0% (0)	25.0% (3)
Blood bilirubin increased	0.0% (0)	16.7% (2)
Hypokalaemia	0.0% (0)	16.7% (2)
Myositis	0.0% (0)	16.7% (2)
Paraesthesia	0.0% (0)	16.7% (2)
Hiccups	0.0% (0)	16.7% (2)

MedDRA/J ver. 17.0
Proportion % (number of subjects)
* No deaths, adverse events that led to treatment discontinuation, or serious adverse drug reactions were reported in either age group.

As shown in Table 10, the incidence of adverse events that were suggestive of cytopenia and alanine aminotransferase (ALT) increased or aspartate aminotransferase (AST) increased tended to be higher in subjects aged ≥6 months and <12 years than in those aged ≥12 years and ≤18 years. Adverse events that are suggestive of cytopenia, ALT increased, and AST increased are known adverse reactions of most antineoplastic agents; therefore, the patients' histories of treatment with antineoplastic agents were investigated.

The proportion of subjects with a history of treatment with antineoplastic agents was higher in subjects aged ≥6 months and <12 years than in those aged ≥12 years and ≤18 years with their respective proportions as follows: 93.3% (14 of 15 subjects) and 41.7% (5 of 12 subjects). Therefore, the differences in the patients' history of treatment with antineoplastic agents may have had an effect on the higher incidence of adverse events that were suggestive of cytopenia, ALT increased, and AST increased in subjects aged ≥6 months and <12 years. The difference in the proportion of subjects with a past medical history or complications of anemia between subjects aged ≥6 months and <12 years (100.0%, 15 of 15 subjects) and those aged ≥12 years and ≤18 years (50.0%, 6 of 12 subjects) may have affected the incidence of anaemia. Of the adverse events that were suggestive of cytopenia, ALT increased, and AST increased, lymphocyte count decreased (non-serious) observed in 1 subject was reported as an adverse drug reaction.

The Japanese phase III study in adults (ONO-7847-01) and foreign pediatric studies (Studies P134, P208, P097) were the studies of fosaprepitant that included the standard treatment group. There was no significant difference in the incidence of adverse events that were suggestive of cytopenia, ALT increased, and AST increased between the standard treatment group and fosaprepitant group in any of these studies. There were no clinically significant trends in the incidence of adverse events including the other events than those described above in the fosaprepitant group compared with the standard treatment group.

3.(iii).B.(2).3) Comparison of Study ONO-7847-03 and the Japanese phase III study in adults (ONO-7847-01)

The applicant compared the incidence of adverse events in the Japanese pediatric study (ONO-7847-03) with that in the Japanese phase III study in adults (ONO-7847-01) of fosaprepitant, and explained the results as follows.

Adverse events with incidence higher in the Japanese pediatric study (ONO-7847-03) than in the Japanese phase III study in adults (ONO-7847-01) by ≥15% were lymphocyte count decreased (96.3% [26 of 27 subjects] in the Japanese pediatric study [ONO-7847-03], 19.5% [34 of 174 subjects] in a Japanese phase III study in adults [ONO-7847-01]; hereinafter the same order applies in this paragraph); neutrophil count decreased (92.6% [25 of 27 subjects], 51.1% [89 of 174 subjects]); white blood cell count decreased (92.6% [25 of 27 subjects], 59.2% [103 of 174 subjects]); anaemia (66.7% [18 of 27 subjects], 1.1% [2 of 174 subjects]); platelet count decreased (59.3% [16 of 27 subjects], 33.3% [58 of 174 subjects]); malaise (48.1% [13 of 27 subjects], 29.3% [51 of 174 subjects]); vomiting (33.3% [9 of 27 subjects], 16.1% [28 of 174 subjects]); and febrile neutropenia (25.9% [7 of 27 subjects], 1.7% [3 of 174 subjects]). All of these adverse events were assumed to be associated with antineoplastic agents. In the Japanese pediatric study (ONO-7847-03), the incidence of adverse events such as cytopenia tended to be higher than that in the Japanese phase III study in adults (ONO-7847-01). It is considered attributable to the fact that more aggressive cancer chemotherapy is performed in pediatric patients despite the risk of adverse reactions of antineoplastic agents because pediatric patients with solid tumors generally have higher sensitivities to antineoplastic agents than adult counterparts have. Furthermore, since the incidence of these adverse events in the fosaprepitant group was comparable to that reported in the standard treatment group in the Japanese phase III study in adults (ONO-7847-01) and foreign pediatric study (P134), there are no specific safety concerns for fosaprepitant. Given that fosaprepitant will be coadministered with antineoplastic agents by physicians who specialize in pediatric chemotherapy, the same caution as for adult patients is considered to be sufficient.

3.(iii).B.(2).4) Post-marketing safety information

The applicant's explanation of the post-marketing safety information of fosaprepitant in and out of Japan:

In the ongoing specified drug use-results survey (the 6th Periodic Safety Update Report [PSUR]: data fixed on March 25, 2015; 2605 adult subjects included) after the market launch of fosaprepitant in Japan,

adverse events have been reported in 41.1% of patients (1070 of 2605 patients) and adverse drug reactions have been reported in 12.4% of patients (323 of 2605 patients). Serious adverse drug reactions have been reported in 13 patients. Adverse drug reactions reported in more than 1 patient were agranulocytosis in 5 patients and neutrophil count decreased in 2 patients (all the outcomes were recovered/resolved).

In the ongoing specified drug use-results survey of aprepitant capsules (the 9th PSUR; data fixed on March 25, 2015; 2999 adult patients and 4 pediatric patients [12 to 18 years] included) in Japan, adverse events have been reported in 52.2% (1564 of 2999 patients) of adult patients and 75.0% (3 of 4 patients) of pediatric patients. Adverse drug reactions have been reported in 10.7% (320 of 2999 patients) of adult patients only. Serious adverse drug reactions have been reported in 16 adult patients only. Adverse drug reactions that were reported in more than 1 patient were neutrophil count decreased in 5 patients, white blood cell count decreased in 3 patients, and hyponatraemia in 3 patients.

In the latest PSUR of fosaprepitant (investigation period: August 14, 2007 to March 25, 2015), common adverse reactions were those suggestive of injection site reaction, anaphylaxis, and cytopenia; precautions concerning these events have already been provided in the Japanese package insert. Adverse drug reactions have been reported in 12 subjects aged <12 years and in 39 subjects aged ≥12 years and ≤18 years in non-Japanese pediatric patients.[20] Common adverse drug reactions reported in pediatric patients were those suggestive of injection site reaction, anaphylaxis, and cytopenia; all of these were the same as the adverse drug reactions reported by adult patients.

On the basis of the above results, there are no pediatric-specific safety concerns compared with adult patients.

PMDA's view:
No clinically significant difference was identified in the incidence of adverse events between subjects aged ≥12 years and ≤18 years in the Japanese pediatric study (ONO-7847-03) and subjects in the Japanese pediatric study of aprepitant capsules (ONO-7436-03). In the Japanese pediatric study (ONO-7847-03), the incidence of adverse events that were suggestive of cytopenia, AST increased, and ALT increased tended to be higher in subjects aged ≥6 months and <12 years than in those aged ≥12 years and ≤18 years. PMDA considers that applicant's explanation regarding the effects of the history of treatment with antineoplastic agents is understandable and that the higher incidence noted poses no significant safety concerns in subjects aged ≥6 months and <12 years. As a result of the comparison with the Japanese phase III study in adults (ONO-7847-01) and the assessment of post-marketing safety information on fosaprepitant, PMDA has determined that fosaprepitant can be administered to pediatric patients providing that the same precautions as those for adult patients are used because no pediatric-specific safety concerns have been found compared with adult patients.

[20] Pediatric use is not approved outside Japan, and these are off-label use results.

3.(iii).B.(3) Indication

Based on the Japanese clinical data, PMDA has determined that the indication for pediatric patients should be "acute or delayed digestive symptoms (nausea and vomiting) resulting from the administration of antineoplastic agents such as cisplatin," the same as that for adults, and a precaution stating "fosaprepitant should only be used when antineoplastic agents including cisplatin, which induce severe nausea and vomiting, are administered" should be provided in the Precautions for Indications section.

3.(iii).B.(4) Dosage and administration

The applicant's rationale for dosage and administration of fosaprepitant in pediatric patients:

3.(iii).B.(4).1) Dosage and administration in infants aged ≥6 months and children aged <12 years

The dosage regimen for pediatric subjects aged ≥6 months and <12 years employed in the Japanese pediatric study (ONO-7847-03) was 3.0 mg/kg, which was the dose estimated to achieve the same aprepitant exposure as that following intravenous administration of 150 mg of fosaprepitant in adult subjects. In the Japanese pediatric study (ONO-7847-03), plasma aprepitant concentrations after intravenous administration of 3.0 mg/kg of fosaprepitant in pediatric subjects aged ≥6 months and <12 years tended to be lower than those after intravenous administration of 150 mg of fosaprepitant in adult subjects (Tables 1 and 2). However, the results in pediatric subjects aged ≥6 months and <12 years in the Japanese pediatric study (ONO-7847-03) demonstrated that the efficacy of fosaprepitant is expected and that there are no significant difference in the safety profile compared with adult subjects and no significant difference in the exposure between subjects who achieved overall phase CR and those who did not. Therefore, administration of fosaprepitant at a dose of >3.0 mg/kg is unlikely to be necessary and there should be no problem with adopting the same dosage regimen as that used in the Japanese pediatric study (ONO-7847-03) for pediatric patients aged ≥6 months and <12 years.

3.(iii).B.(4).2) Dosage and administration in adolescent patients aged ≥12 years and ≤18 years

The dosage regimen for adolescents aged ≥12 years and ≤18 years in the Japanese pediatric study (ONO-7847-03) was 150 mg of fosaprepitant intravenously administered, which was determined based on the fact that the dosage and administration of aprepitant capsule for adolescents aged ≥12 years and ≤18 years is the same as that for adults. The results of the Japanese pediatric study (ONO-7847-03) demonstrated that the efficacy of fosaprepitant is expected and there are no different trends in the safety profile compared with those in adult subjects, thus there should be no problem with adopting the dosage and administration for adult patients as that for adolescent patients aged ≥12 years and ≤18 years.

PMDA's view:

The results of the Japanese pediatric study (ONO-7847-03) have shown the efficacy is expected and the safety is acceptable [see "3.(iii).B.(1) Efficacy" and "3.(iii).B.(2) Safety"], thus PMDA has considered it appropriate to select the dose of 3.0 mg/kg for pediatric patients aged ≥6 months and <12 years according to the Japanese study. Outside Japan, a clinical study that includes a fosaprepitant 5.0 mg/kg

group is currently being conducted in pediatric subjects aged <12 years.[21] If foreign clinical data suggest the need for 5.0 mg/kg, the dose in Japan should also be evaluated based on information collected by the post-marketing surveillance. PMDA considers that no problems should arise from administering fosaprepitant over 60 minutes, according to the Japanese study.

The results of the Japanese pediatric study (ONO-7847-03) have demonstrated the efficacy is expected and the safety is acceptable in adolescents aged ≥12 years and ≤18 years [see "3.(iii).B.(1) Efficacy" and "3.(iii).B.(2) Safety"]. PMDA has determined that the dosage and administration for adult patients should be adopted as that for adolescent patients aged ≥12 years and ≤18 years.

The Precautions for Dosage and Administration section for adults state that, in principle, fosaprepitant should be coadministered with corticosteroids and 5-HT_3 receptor antagonists and that the corticosteroid dose should be appropriately reduced in consideration of the drug interactions of fosaprepitant with corticosteroids. These provisions also apply to pediatric patients and the same precautions as those for adult patients should be provided.

The dosage and administration of fosaprepitant will be finalized, taking into account the comments made in the Expert Discussion.

[21] No difference was found in the delayed phase CR rate after administration of fosaprepitant at 3.0 mg/kg in subjects aged ≥6 months and <12 years compared with that in the standard treatment group in the foreign pediatric study (P134) (18.2% in fosaprepitant group; 15.8% in standard therapy group). Thus, the study currently being conducted includes fosaprepitant 5.0 mg/kg group additionally.

3.(iii).B.(5) Post-marketing investigations

The applicant plans a specified drug use-results survey as shown in Table 11.

Table 11. Outline of specified drug use-results survey (draft)

Objectives	**To understand the occurrence of adverse events and adverse reactions of fosaprepitant in pediatric patients with malignant tumors, and investigate factors considered to affect the safety and efficacy.**
Method	**Central registration method**
Survey period	**Approximately 2 years and 6 months (observation period is up to 8 cycles for each patient)**
Planned number of patients	**100 patients (number of patients for analysis: 50 patients)**
Planned number of study sites	**10 to 20 sites**
Target patients	**Patients aged ≥6 months and <15 years**
Main survey items	**• Patient characteristics (age, sex, height, body weight, performance status, types of carcinoma, antineoplastic regimen, history of anticipatory nausea and vomiting in the past regimens, motion sickness, medical history of other diseases than cancer, etc.) • Medication status of fosaprepitant and concomitant drugs (antiemetic agents, antineoplastic agents, other concomitant drugs): dosage, duration of treatment, etc. • presence or absence of concomitant therapy (if any, details) • Efficacy: presence/absence of vomiting and presence/absence of nausea (observation period: acute phase [Day 1]; delayed phase [between Days 2 and 5]) • Adverse events (including abnormal laboratory values) [Key survey items] • Safety in patients who received fosaprepitant in ≥2 cycles • Occurrence of injection site disorder and hypersensitivity • Concentrations of fosaprepitant administered and infusion time**

PMDA has determined that there should be no significant problem with the draft outline of the plan proposed by the applicant. However, it will be finalized, taking into account the comments made in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment of the data submitted in the new drug application were conducted 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. The inspection and assessment revealed no particular problems. PMDA thus concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection of the data submitted in the new drug application (5.3.5.2-1) was conducted 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. The inspection revealed no particular problems. PMDA thus concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of fosaprepitant in the treatment of pediatric patients aged ≥6 months is expected and its safety is acceptable in view of its observed benefits. This application may be approved if fosaprepitant is not considered to have any particular problems on efficacy, safety, indication, dosage and administration, and survey items of post-marketing surveillance based on comments from the Expert Discussion.

Review Report (2)

February 4, 2016

I. Product Submitted for Registration

[Brand name]	Proemend for Intravenous Infusion 150 mg
[Non-proprietary name]	Fosaprepitant Meglumine
[Applicant]	Ono Pharmaceutical Co., Ltd.
[Date of application]	May 27, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, 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).

PMDA's conclusions regarding the efficacy, safety, indication, dosage and administration, and post-marketing investigations are described in Review Report (1). The following comments were raised on the efficacy, indication, and dosage and administration while the conclusions regarding the safety specification and post-marketing investigations were supported.

(1) Efficacy

The following comments were raised from the expert advisors concerning PMDA's conclusions shown in Review Report (1), and the PMDA's conclusion was supported.

- Although the statistical evaluation is difficult, there is no objection to PMDA's conclusion that fosaprepitant is expected to be effective in pediatric patients, based on the comprehensive consideration of the results of the Japanese and foreign pediatric studies and the necessity of fosaprepitant for pediatric patients who have difficulty taking aprepitant capsules. However, due to the limited number of subjects evaluated in clinical studies, it is necessary to collect more safety information through post-marketing surveillance etc.

(2) Indication

The following comments were raised from the expert advisors concerning PMDA's conclusion shown in Review Report (1).

- There is no objection to PMDA's conclusion to adopt the same indication as that approved for adults.
- Recently, the guidelines for antiemetic agents have been issued in Japan, and antiemetic agents are becoming widely used according to the category of emetogenic risk of anticancer drugs in the clinical

setting. Antineoplastic agents that may be coadministered with fosaprepitant should be specified as moderately or highly emetogenic in the indications for both pediatric and adult use.

PMDA's view:
The comments from the expert advisors regarding description of the category of emetogenic risk of antineoplastic agents in the Indication is related not only to pediatric use, but also to adult use and further to other antiemetic agents. Therefore, PMDA will review this matter, taking account of common practice in the clinical setting after market launch and beyond.

In summary, at present, PMDA concluded that the "Indication" and "Precautions for Indications" of fosaprepitant in pediatric patients should be the same as those approved for adult patients as shown below.

[Indication]
Acute or delayed digestive symptoms (nausea and vomiting) resulting from the administration of antineoplastic agents such as cisplatin

[Precautions for Indications]
Fosaprepitant should only be used when antineoplastic agents including cisplatin, which induce severe nausea and vomiting, are administered.

(No change from the existing approval)

(3) Dosage and administration
The following comments were raised from the expert advisors concerning PMDA's conclusion shown in Review Report (1), and PMDA's conclusion was supported.

- At present, the expert advisors do not object to setting the dosage and administration in pediatric patients aged ≥6 months and <12 years to 3.0 mg/kg, which had been evaluated in the Japanese pediatric study. Since plasma aprepitant concentrations after administration of fosaprepitant tended to be lower in pediatric patients aged ≥6 months and <12 years, it is recommended to evaluate the dose when data on the 5.0 mg/kg dosage, which is currently being evaluated in the ongoing foreign pediatric study, become available.

PMDA requested that the applicant modify the "Dosage and Administration" and "Precautions for Dosage and Administration" of fosaprepitant in pediatric patients as shown below, based on the above comment. The applicant modified the relevant parts appropriately, and PMDA accepted the revised descriptions.

[Dosage and Administration]
- Adults and adolescents aged ≥12 years

  The usual dosage for adults and adolescents aged ≥12 years is 150 mg of fosaprepitant administered

as an intravenous infusion once on the first day of antineoplastic administration, in combination with other antiemetic agents.

- Infants aged ≥6 months and children aged <12 years

  The usual dosage for infants aged ≥6 months and children aged <12 years is 3.0 mg/kg of fosaprepitant administered as an intravenous infusion once on the first day of antineoplastic administration, in combination with other antiemetic agents.

  A single dose of fosaprepitant should not exceed 150 mg.

[Precautions for Dosage and Administration]

- Fosaprepitant should be coadministered with corticosteroids and 5-HT_3 receptor antagonistic antiemetic agents in principle. Concomitant corticosteroids and 5-HT_3 receptor antagonistic antiemetic agents should be administered in reference to the latest information on the dosage and administration shown in their package inserts, etc. The corticosteroid dose should be appropriately reduced in consideration of the drug interactions of fosaprepitant or the active form aprepitant with corticosteroids.
- The administration of fosaprepitant increases the frequency of injection site disorder when the infusion speed or infusion concentration is increased. Therefore, reconstitute 1 vial of fosaprepitant (150 mg) with 5 mL of saline, and infuse it intravenously as instructed below.
- Adults and adolescents aged ≥12 years

  Reconstitute fosaprepitant with saline to make the final volume of 100 to 250 mL (final concentration, 0.6 to 1.5 mg/mL) and infuse it intravenously for 30 minutes, starting 1 hour before the administration of antineoplastic agents.
- Infants aged ≥6 months and children aged <12 years

  Reconstitute fosaprepitant (3.0 mg/kg) with saline to make fosaprepitant solution at the final concentration of 0.6 to 1.5 mg/mL, and infuse it intravenously for 60 minutes, starting 1.5 hours before the administration of antineoplastic agents.

(The underline denotes added text.)

(4) Draft risk management plan

PMDA concluded that the safety and efficacy specifications shown in Table 12 should be included in the current draft risk management plan and that the additional pharmacovigilance and risk minimization activities shown in Table 13, as well as a specified drug use-results survey shown in Table 14, should be performed.

Table 12. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risk	**Important potential risk**	**Important missing information**
• Mucocutaneous ocular syndrome • Shock, anaphylaxis • Injection site disorder	• Drug interactions with hormonal contraceptives (ethinyl estradiol etc.) • Perforated duodenal ulcer	Not applicable
Efficacy specification • Efficacy in administration in multiple cycles • Efficacy in pediatric use		

Table 13. Outline of additional pharmacovigilance and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance actions	Additional risk minimization activities
• Specified drug use-results survey in long-term administration in adults • Specified drug use-results in pediatric use	• Not applicable

Table 14. Outline of the specified drug use-results survey plan (draft)

Objectives	To understand the occurrence of adverse events and adverse reactions of fosaprepitant in pediatric patients with malignant tumors, and investigate factors considered to affect the safety and efficacy.
Method	Central registration method
Survey period	Approximately 2 years and 6 months (observation period is up to 8 cycles for each patient)
Planned number of patients	100 patients
Planned number of study sites	20 to 40 sites
Target patients	Patients aged ≥6 months and ≤18 years
Main survey items	• Patient characteristics (age, sex, height, body weight, performance status, types of carcinoma, antineoplastic regimen, history of anticipatory nausea and vomiting in the past regimens, motion sickness, medical history of other diseases than cancer, etc.) • Medication status of fosaprepitant and concomitant drugs (antiemetic agents, antineoplastic agents, other concomitant drugs): dosage, duration of treatment, etc. • Efficacy: presence/absence of vomiting and nausea (observation period: acute phase [Day 1]; delayed phase [between Days 2 and 5]) • Adverse events (including abnormal laboratory values) <Priority investigation items> • Safety in patients who received fosaprepitant in ≥2 cycles • Occurrence of injection site disorder and hypersensitivity • Effects of concentrations of fosaprepitant administered and infusion time on safety

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and dosage and administration statements as shown below, on the following condition for approval. As the application seeks approval of new dosages for an approved drug, PMDA determines that a re-examination period of 4 years is appropriate with respect to the proposed dosage and administration.

[Indications] Acute or delayed digestive symptoms (nausea and vomiting) resulting from the administration of antineoplastic agents such as cisplatin

[Dosage and administration]

- Adults and adolescents aged ≥12 years

  The usual dosage for adults and adolescents aged ≥12 years is 150 mg of fosaprepitant administered as an intravenous infusion once on the first day of antineoplastic administration, in combination with other antiemetic agents.
- Infants aged ≥6 months and children aged <12 years

The usual dosage for infants aged ≥6 months and children aged <12 years is 3.0 mg/kg of fosaprepitant administered as an intravenous infusion once on the first day of antineoplastic administration, in combination with other antiemetic agents.

A single dose of fosaprepitant should not exceed 150 mg.

(The underline denotes added text.)

[Condition for approval] The applicant is required to develop and appropriately implement a risk management plan.