

Review Report

October 9, 2015
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]	Kenketu Glovenin-I for I.V. Injection 500 mg, Kenketu Glovenin-I for I.V. Injection 2500 mg, Kenketu Glovenin-I for I.V. Injection 5000 mg
[Non-proprietary name]	Freeze-dried Polyethylene Glycol Treated Human Normal Immunoglobulin
[Applicant]	Nihon Pharmaceutical Co., Ltd.
[Date of application]	December 25, 2014
[Dosage form/Strength]	Lyophilized powder for solution for injection: Each vial contains 500, 2500, or 5000 mg of Polyethylene Glycol Treated Human Normal Immunoglobulin G.
[Application classification]	Prescription drug, (4) Drug with a new indication
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug I

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Review Results

October 9, 2015

[Brand name] Kenketu Glovenin-I for I.V. Injection 500 mg,
Kenketu Glovenin-I for I.V. Injection 2500 mg,
Kenketu Glovenin-I for I.V. Injection 5000 mg

[Non-proprietary name] Freeze-dried Polyethylene Glycol Treated Human Normal
Immunoglobulin

[Applicant] Nihon Pharmaceutical Co., Ltd.

[Date of application] December 25, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with bullous pemphigoid who have not sufficiently responded to corticosteroids has been demonstrated 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.

[Indication]

1. Agammaglobulinemia or hypogammaglobulinemia
2. Coadministration with antibiotics for the treatment of severe infection
3. Idiopathic thrombocytopenic purpura (ITP) (for patients with ITP unresponsive to other drugs who have a marked bleeding tendency and who require temporary hemostasis during emergency procedures including surgery and delivery)
4. Kawasaki disease (KD) in the acute phase (for patients with severe KD who have a risk of coronary artery disorder)
5. Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)
6. Pemphigus (for patients with pemphigus inadequately responsive to corticosteroids)
7. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (for patients with SJS or TEN inadequately responsive to corticosteroids)
8. Bullous pemphigoid (BP) (for patients with BP inadequately responsive to corticosteroids)

(Underline denotes additions.)

[Dosage and administration] The product 500 mg should be reconstituted with 10 mL of the supplied solvent (Water for Injection [the Japanese Pharmacopoeia]). The reconstituted solution should be administered according to the regimens specified below for each indication. Direct intravenous injection should be given at a very slow rate.

Agammaglobulinemia or hypogammaglobulinemia:

The usual dosage of human immunoglobulin G is 200 to 600 mg (in 4-12 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection once every 3 to 4 weeks. The dose may be adjusted according to the patient's condition.

Coadministration with antibiotics for the treatment of severe infection:

The usual dosage of human immunoglobulin G is 2500 to 5000 mg (in 50-100 mL) for adults, and 100 to 150 mg (in 2-3 mL)/kg body weight for children, administered by an intravenous infusion or a direct intravenous injection. The dose may be adjusted according to the patient's condition.

Idiopathic thrombocytopenic purpura:

The usual daily dosage of human immunoglobulin G is 200 to 400 mg (in 4-8 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection. If symptoms do not improve after 5-day intravenous immunoglobulin treatment, the treatment should be discontinued. The dose may be adjusted according to the patient's age and condition.

Kawasaki disease in the acute phase:

The usual dosage of human immunoglobulin G is 200 mg (in 4 mL)/kg body weight administered once daily for 5 days by an intravenous infusion or a direct intravenous injection, or 2000 mg (in 40 mL)/kg body weight administered by a single intravenous infusion. The dose for 5-day administration may be decreased or increased according to the patient's age and condition, and the dose for single-dose administration may be decreased according to the patient's age and condition.

Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy):

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion or a direct intravenous injection. The dose may be decreased according to the patient's age and condition.

Pemphigus:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion. The dose may be decreased according to the patient's age and condition.

Stevens-Johnson syndrome and toxic epidermal necrolysis:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

Bullous pemphigoid:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

(Underline denotes added text.)

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

Review Report (1)

September 7, 2015

I. Product Submitted for Registration

[Brand name]	Kenketu Glovenin-I for I.V. Injection 500 mg, Kenketu Glovenin-I for I.V. Injection 2500 mg, Kenketu Glovenin-I for I.V. Injection 5000 mg
[Non-proprietary name]	Freeze-dried Polyethylene Glycol Treated Human Normal Immunoglobulin
[Applicant]	Nihon Pharmaceutical Co., Ltd.
[Date of application]	December 25, 2014
[Dosage form/Strength]	Lyophilized powder for solution for injection: Each vial contains 500, 2500, or 5000 mg of Polyethylene Glycol Treated Human Normal Immunoglobulin G
[Proposed indication]	<ol style="list-style-type: none">1. Agammaglobulinemia or hypogammaglobulinemia2. Coadministration with antibiotics for the treatment of severe infection3. Idiopathic thrombocytopenic purpura (ITP) (for patients with ITP unresponsive to other drugs who have a marked bleeding tendency and who require temporary hemostasis during emergency procedures including surgery and delivery)4. Kawasaki disease (KD) in the acute phase (for patients with severe KD who have a risk of coronary artery disorder)5. Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)6. Pemphigus (for patients with pemphigus inadequately responsive to corticosteroids)7. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (for patients with SJS or TEN inadequately responsive to corticosteroids)8. <u>Bullous pemphigoid (BP) (for patients with BP inadequately responsive to corticosteroids)</u> <p>(Underline denotes additions.)</p>
[Proposed dosage and administration]	

The product 500 mg should be reconstituted with 10 mL of the supplied solvent (Water for Injection [the Japanese Pharmacopoeia]). The reconstituted solution should be administered according to the regimens specified below for each indication. Direct intravenous injection should be given at a very slow rate.

Agammaglobulinemia or hypogammaglobulinemia:

The usual dosage of human immunoglobulin G is 200 to 600 mg (in 4-12 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection once every 3 to 4 weeks. The dose may be adjusted according to the patient's condition.

Coadministration with antibiotics for the treatment of severe infection:

The usual dosage of human immunoglobulin G is 2500 to 5000 mg (in 50-100 mL) for adults, and 100 to 150 mg (in 2-3 mL)/kg body weight for children, administered by an intravenous infusion or a direct intravenous injection. The dose may be adjusted according to the patient's condition.

Idiopathic thrombocytopenic purpura:

The usual daily dosage of human immunoglobulin G is 200 to 400 mg (in 4-8 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection. If symptoms do not improve after 5-day intravenous immunoglobulin treatment, the treatment should be discontinued. The dose may be adjusted according to the patient's age and condition.

Kawasaki disease in the acute phase:

The usual dosage of human immunoglobulin G is 200 mg (in 4 mL)/kg body weight administered once daily for 5 days by an intravenous infusion or a direct intravenous injection, or 2000 mg (in 40 mL)/kg body weight administered by a single intravenous infusion. The dose for 5-day administration may be decreased or increased according to the patient's age and condition, and the dose for single-dose administration may be decreased according to the patient's age and condition.

Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy):

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion or a direct intravenous injection. The dose may be decreased according to the patient's age and condition.

Pemphigus:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion. The dose may be decreased according to the patient's age and condition.

Stevens-Johnson syndrome and toxic epidermal necrolysis:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

Bullous pemphigoid:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive day by an intravenous infusions.

(Underline denotes additions.)

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 has been filed for a new indication and, the submitted data set does not include "Data relating to quality" and some of "Non-clinical data" (i.e., pharmacokinetic and toxicological study results).

1. Origin or history of discovery and usage conditions in foreign countries, etc.

Bullous pemphigoid is an autoimmune bullous disease with subepidermal blisters caused by autoantibody against antigens in the epidermal basement membrane. Clinically, the disease is characterized by diffuse pruritic erythema and tense blisters on the skin. In Japan, there are

approximately 6850 patients with pemphigoid, which includes both bullous and non-bullous pemphigoid, with the majority considered to be the elderly.¹

Moderate to severe bullous pemphigoid is basically treated with oral corticosteroids. Currently, no immunoglobulin preparations, including the proposed product, are approved for the indication of bullous pemphigoid in Japan or in other countries. However, it has been reported in and outside Japan² that high-dose intravenous immunoglobulin (IVIG) therapy is administered to patients who are inadequately responsive to corticosteroids. Clinical practice guidelines used in some countries such as the US, the UK, and Canada, etc., include IVIG therapy for the treatment of bullous pemphigoid.³ Also, the clinical practice guideline of Japan⁴ includes IVIG therapy for the treatment of intractable bullous pemphigoid. In April 2014, the Japanese Dermatological Association submitted a request to the Minister of the Health, Labour and Welfare for extension of the indications of freeze-dried PEG-treated human normal immunoglobulin to include treatment of patients with bullous pemphigoid inadequately responsive to corticosteroids.

Kenketu Glovenin-I for I.V. Injection 500 mg, Kenketu Glovenin-I for I.V. Injection 2500 mg, and Kenketu Glovenin-I for I.V. Injection 5000 mg (hereinafter collectively referred to as “HNIG”) are solutions for injections containing freeze-dried polyethylene glycol treated human normal immunoglobulin as the active ingredient. In Japan, HNIG was approved for the indications of “agammaglobulinemia or hypogammaglobulinemia” and “coadministration with antibiotics for the treatment of severe infection” in October 1984, followed by approval for indications of “idiopathic thrombocytopenic purpura (for patients with ITP unresponsive to other drugs who have a marked bleeding tendency and who require temporary hemostasis during emergency procedures including surgery and delivery,” “Kawasaki disease in the acute phase (for patients with severe KD who have a risk of coronary artery disorder,” “improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy),” “pemphigus (for patients with pemphigus inadequately responsive to corticosteroids),” and “Stevens-Johnson syndrome and toxic epidermal necrolysis (for patients with SJS or TEN inadequately responsive to corticosteroids).”

With this as the background, the applicant conducted clinical studies in patients with bullous pemphigoid inadequately responsive to steroid therapy, and submitted this partial change application based on the results of the studies together with the above literature and guidelines published in and outside Japan.

2. Non-clinical data

2.(i) Summary of pharmacology studies

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

The applicant submitted the results from primary pharmacodynamics studies, namely the studies on *in vivo* effect of HNIG in a passive transfer mouse model of bullous pemphigoid (BP) and in an active BP mouse model.

¹ Website of the Ministry of Health, Labour and Welfare “Intractable diseases newly designated on July 1, 2015” (<http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000085261.html>, accessed on July 17, 2015)

² *Acta Derm Venereol.* 2013;93:346-349, *Eur J Dermatol.* 2012;22:363-369, etc.

³ *Arch Dermatol.* 2003;139:1051-1059, *Br J Dermatol.* 2012;167:1200-1214, *J Cutan Med Surg.* 2006;10:205-221, etc.

⁴ Research Project on Rare and Intractable Dermatological Diseases “Clinical Practice Guideline 2008” supported by Health and Labour Sciences Research Grants (The research on rare and intractable dermatological diseases. General Partial Research Report FY 2007. Integrated Research Report FY 2005 to 2007)

2.(i).A.(1) Primary pharmacodynamics

2.(i).A.(1).1 Effect of immunoglobulin in a passive transfer mouse model of BP (4.2.1.1-1, Study 011)

A single dose of HNIG 400 or 2000 mg/kg or physiological saline was administered intraperitoneally to a passive transfer mouse model of BP⁵ at 2 hours before SG-IgG⁶ administration. Table 1 shows the epidermolysis rate and blood anti-BP180⁷ antibody titer at 18 hours after SG-IgG administration.

The epidermolysis rate was not significantly different between both HNIG groups and the disease control group (physiological saline group), whereas epidermolysis tended to be suppressed in the HNIG 2000 mg/kg group. Blood anti-BP180 antibody titer was significantly lower in both HNIG groups than the disease control group.

Table 1. Epidermolysis rate and blood anti-BP180 antibody titer in a mouse model of passive transfer BP

Treatment group	Epidermolysis rate	Blood anti-BP180 antibody titer
Disease control	100% (10/10)	1.04 ± 0.28
HNIG 400 mg/kg	100% (10/10)	0.76 ± 0.15*
HNIG 2000 mg/kg	70% (7/10)	0.66 ± 0.18*

n = 10, mean ± standard deviation (SD)

* P < 0.05 (vs. disease control group; t-test)

2.(i).A.(1).2 Effect of HNIG in an active BP mouse model (4.2.1.1-2, Study 003)

HNIG 400 or 2000 mg/kg or physiological saline was injected to the caudal vein of an active BP mouse model⁸ once daily for 21 consecutive days. Table 2 shows disease score⁹ on Day 35 and blood anti-BP180 antibody titer on Days 11, 18, and 21.

Disease score on Day 35 was not significantly different between both HNIG groups and the disease control group (i.e., physiological saline group) but tended to decrease dose-dependently in the HNIG groups. Blood anti-BP 180 antibody titer significantly decreased in the HNIG 2000 mg/kg group on Day 11 and in the HNIG 400 and 2000 mg/kg groups on Day 18 compared with the disease control group, whereas no significant decrease was observed in either HNIG group on Day 21.

Histopathological examination¹⁰ was performed on Day 35. Inflammatory cell infiltration and crust formation in the back skin were reduced in both HNIG groups compared with the disease control group, whereas no marked difference was observed in the auricle or in the skin of the anterior neck.

Table 2. Disease score and blood anti-BP180 antibody titer in an active BP mouse model

Treatment group	Disease score	Blood anti-BP180 antibody titer		
		Day 11	Day 18	Day 21
Disease control	55.5 ± 10.5	1455.9 ± 436.1	911.4 ± 268.0	680.9 ± 250.6
HNIG 400 mg/kg	40.1 ± 30.1	1121.8 ± 526.8	597.2 ± 358.4*	589.2 ± 348.8
HNIG 2000 mg/kg	37.4 ± 16.7	937.8 ± 364.8*	558.8 ± 348.4*	623.8 ± 376.3

n = 9 to 11, mean ± SD

* P < 0.05 (vs. disease control group; one-way analysis of variance)

⁵ A single dose of SG-IgG 30 µL/g (prepared to a concentration of 5 µg/µL) was injected intraperitoneally to BP180-humanized neonatal mice to transiently induce bullous pemphigoid (passive immunization).

⁶ Mouse-derived pathologic IgG obtained after purification and concentration of IgG isolated from wild-type mice immunized by grafting the epidermis of human BP180-expressing mice (*J Invest Dermatol.* 2007;127:2807-2817)

⁷ Type XVII collagen which is a structural protein of the epidermal basement membrane

⁸ Spleen cells of wild-type mice immunized by grafting the epidermis of human BP180-expressing mice were injected into the caudal vein of BP180-humanized immunodeficient mice to maintain the production of the pathologic antibody in the body, thereby inducing bullous pemphigoid (*J Immunol.* 2010;184:2166-2174).

⁹ Disease score was calculated as the sum of the products of “the fractional injured surface area in each organ relative to the body surface area” and “the assigned score in each organ” (score assigned to each organ: ear [5], oronasal area [5], head and neck area including periocular area [10], forelimbs [10], hind limbs [20], tail [10], trunk [40]).

¹⁰ The extent of inflammatory cell infiltration, epidermal thickening, ulcer, crust, and epidermolysis in each tissue (auricle, skin of the anterior neck, back skin) was evaluated using a 5-point scale.

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

Pharmacological effect

The applicant's explanation on the pharmaceutical effect of HNIG:

The mechanism of action of HNIG against bullous pemphigoid has not been elucidated. However, given that bullous pemphigoid is an autoimmune bullous disease with subepidermal blisters caused by the autoantibody in the epidermal basement membrane with BP180 as the primary antigen, HNIG is considered to exhibit its effect by a similar mechanism found in other autoimmune diseases. The following findings were reported regarding the mechanism of action of a high-dose intravenous immunoglobulin (IVIG) therapy:¹¹

- When IgG acts on inhibitory Fcγ receptors expressed on B cells, B cell activity is suppressed, resulting in decreased antibody production.
- Neonatal Fc receptor (FcRn) involved in recycling blood IgG, and IgG bound to the receptor is released into the blood again without being degraded within the cell. When FcRn is fully saturated by a high dose of IgG, degradation of autoantibody (SG-IgG used in the study submitted in this application) is enhanced.

Considering the above findings, the decreased blood anti-BP180 antibody titer accompanied by delayed disease progression and improvement in symptoms observed in the primary pharmacodynamic studies submitted in this application is presumed to be mainly attributable to the inhibitory effect of HNIG on B-cell antibody production and on FcRn-mediated recycling of IgG antibodies.

In the submitted study using a passive transfer mouse model of BP, no significant difference in the epidermolysis rate was observed between the HNIG groups and the disease control group.

The applicant's explanation on the reason for no significant difference in the above-mentioned study: In this mouse model, binding of SG-IgG to BP180 is considered to induce inflammatory reactions leading to degradation of BP180 and, if the expression level of BP180 decreases below the level necessary to maintain the strength of the epidermis, epidermolysis will occur. Although anti-BP180 antibody titer was decreased in both HNIG groups, the expression level of BP180 had decreased below the level necessary to maintain the strength of the epidermis, resulting in the failure of HNIG to prevent epidermolysis.

PMDA asked the applicant to explain why there were no significant difference between HNIG groups and the disease control group in the disease score on Day 35 and in blood anti-BP180 antibody titer on Day 21 in the study using an active BP mouse model.

The applicant's response:

Disease score slightly improved in both HNIG groups compared with the disease control group but the difference was not statistically significant because of the greater variability than expected from the results of the preliminary study. The blood anti-BP180 antibody titer in the disease control group reached a peak on Day 11 and then decreased over time, resulting in a reduced absolute level of anti-BP180 antibody on Day 21, because of which there were no differences between the HNIG groups and the disease control group.

The histopathological examination in the study using an active BP mouse model revealed that inflammatory cell infiltration and crust formation in the back skin were reduced in the HNIG group compared with the disease control group, whereas no marked difference was observed either in the auricle or in the skin of the anterior neck. PMDA asked the applicant to explain the reason for the discrepancy.

The applicant's response:

In this mouse model, the auricle and the skin of the anterior neck seem to be the regions which are highly prone to lesions. The mouse auricle has only a thin dermis and no hair. The body area is within reach by the forelimb, and thus is susceptible to self-scratching. The mouse auricle therefore tends to evoke a

¹¹ *N Engl J Med.* 2012;367:2015-2025.

strong inflammatory reaction. As a result, lesions in the auricle and the skin of the anterior neck resulted in severe tissue injury on Day 35, precluding the effect of HNIG. The extent of the histopathological evaluation at each site tended to be roughly similar to that of the disease score at the same site. Also, the disease score in the auricle on Day 14 was lower in the HNIG group than the disease control group, showing a tendency of suppressed disease progression. These results suggest the possibility that HNIG would have been effective in the auricle and the skin of the anterior neck as well if the histopathological examination had been performed before the lesions became severe. In contrast, HNIG was effective in the back skin because of the difficulty for mice to reach and scratch by limbs.

PMDA's view:

The submitted study data has demonstrated that the administration of HNIG, a formulation containing a high dose of IgG, decreases the titer of the pathologic antibody in blood. Although the submitted data on studies using the passive transfer mouse model of BP and active BP mouse model did not show significant improvement in disease conditions in the HNIG groups compared with the disease control group, the discussion of the applicant is acceptable. The HNIG groups showed a tendency for improvement to a certain extent. Given that bullous pemphigoid is an autoimmune skin disease caused by the pathogenic autoantibody resulting in tissue injury, HNIG is expected to improve disease conditions of patients with bullous pemphigoid by its activity to decrease the pathogenic antibody level.

3. Clinical data

3.(i) Summary of biopharmaceutical studies, associated analytical methods, and clinical pharmacology studies

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

No new data were submitted from biopharmaceutical studies, associated analytical methods, or clinical pharmacology studies.

3.(ii) Summary of clinical efficacy and safety

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

The applicant submitted the efficacy and safety evaluation data, namely the results of a Japanese phase II study (NPB-01-06/E-01) and a Japanese phase III study (NPB-01-06/C-01).

In both studies, clinical symptoms of patients were evaluated using "clinical symptom score" (Table 3).

**Table 3. Clinical symptoms score
(modified criteria for assessing the severity of bullous pemphigoid ^{a)})**

Item Score	Area of skin lesion ^{b)} (sum of the areas of blisters, erosions, and erythemata)	Number of new blisters/day
0	None	None
1	<5%	Occasionally ^{c)}
2	≥5% and <15%	1-4
3	≥15%	≥5

a) Research Project on Rare and Intractable Dermatological Diseases "Clinical Practice Guideline 2008" supported by Health and Labour Sciences Research Grants (The survey on rare intractable diseases. General Partial Research Report FY 2007. Integrated Research Report FY 2005 to 2007, attached document 1. March 2008, p. 17)

b) Percentage of the entire body surface area

c) New blisters occurred occasionally, but not every day, in a week.

"Pemphigus Disease Area Index (PDAI) score" was used to evaluate efficacy in both studies (Table 4).

Table 4. PDAI score

	Skin	Scalp	Mucosal membrane
Anatomical location	(12 sites) Ears, nose, rest of the face, neck, chest, abdomen, back/buttocks, arms, hands, legs, feet, genitals	(1 site) Scalp	(12 sites) Eyes, nasal cavity, buccal mucosa, hard palate, soft palate, upper gingiva, lower gingiva, tongue, floor of mouth, labial mucosa, posterior pharynx, anogenital
Score	(erosion/blister or new erythema) 0: Absent 1: 1 to 3 lesions, up to one >2 cm in any diameter 2: 2 to 3 lesions, at least two >2 cm in diameter 3: >3 lesions, none >6 cm in diameter 5: >3 lesions, and/or at least one >6 cm in diameter 10: >3 lesions, and/or at least one >16 cm in diameter or the entire area	(erosion/blister or new erythema) 0: Absent 1: Localized in one quadrant 2: Localized in two quadrants 3: Localized in three quadrants 4: Affects the whole skull 10: At least one lesion ≥6 cm in diameter	(erosion/blister) 0: Absent 1: 1 lesion 2: 2 to 3 lesions 5: >3 lesions, or at least two lesions >2 cm in diameter 10: The entire area

	Erosion/blister	New erythema	Erosion/blister or new erythema
Skin	A1	A2	A3
Scalp	B1	B2	B3
Mucosal membrane	C	-	-

Note: Scores A to C are the sum of the scores of each site.
PDAI score = A3 + B3 + C (phase II and phase III studies)
 “Erosion/blister” score in PDAI = A1 + B1 + C (phase III study)
 “New erythema” score in PDAI = A2 + B2 (phase III study)

3.(ii).A.(1) Japanese phase II study (5.3.5.1-1, Study NPB-01-06/E-01 [■ 20■ to ■ 20■])

A multi-center, randomized, double-blind, parallel group, placebo-controlled study in patients¹² aged ≥20 years (target sample size, 20) with bullous pemphigoid showing no improvement in clinical symptoms with steroid therapy¹³ (both clinical symptom scores of ≥1 point [Table 3])¹⁴ was conducted in 16 centers in Japan to investigate the efficacy and safety of HNIG in an exploratory manner.

HNIG (400 mg/kg) or placebo was administered by intravenous infusion once daily for 5 days (study drug treatment period), followed by a post-dose observation period (from the start of treatment to Week 8) and by a follow-up period (Weeks >8 to 24). Plasmapheresis and steroid pulse therapy were prohibited from the beginning of the run-in period (7-14 days) through the end of the post-dose observation period, but were allowed after “protocol-off.”¹⁵

A total of 22 patients were treated (12 patients in the placebo group, 10 patients in the HNIG group) and all of them were included in the full analysis set (FAS), the per protocol set (PPS), and the safety analysis set. The FAS and PPS were subjected to efficacy analysis. Two patients in the HNIG group discontinued the study during the follow-up period because of “death” and “uncertainty of future visits” (1 patient each).

The efficacy of HNIG treatment was assessed by “sum of the PDAI scores on Day 1 (the study drug treatment period) and those on Day 15 and Day 57 (the post-dose observation period).” The results are shown in Table 5. The “Protocol-off” rate on Day 57 during the post-dose observation period was 33.3% (4 of 12 patients) in the placebo group and 10.0% (1 of 10 patients) in the HNIG group.

¹² Patients with continued treatment of bullous pemphigoid (e.g., corticosteroids including topical drugs, immunosuppressants, tetracycline, minocycline, nicotinamide, diaminodiphenyl sulfone [DDS]) without any addition or change to the therapy after informed consent

¹³ Treatment at prednisolone-equivalent doses of ≥20 mg/day

¹⁴ Patients who had both clinical symptom scores of ≥1 point on Day 1 of the run-in period and who met the criteria 1) and 2) below when observed values were compared between Day 1 and the last day of the pre-dose observation period.

1) The observed area of skin lesion remained unchanged or increased, 2) the observed number of blisters remained unchanged or increased.

¹⁵ In the event of no change or aggravation of clinical symptoms, the time point when the investigator or subinvestigator decided that there is no other way but to give more intensive treatment

Table 5. Sum of PDAI scores^{a)} on Day 1 in the study drug treatment period and those on Day 15 and Day 57 in the post-dose observation period (FAS)

		Placebo (n = 12)		HNIG (n = 10)	
		Observed value	Change from Day 1	Observed value	Change from Day 1
Study drug treatment period	Day 1	39.8 ± 22.8	-	25.6 ± 25.1	-
	Day 15	24.9 ± 28.9	-14.9 ± 21.9	5.40 ± 7.75	-20.2 ± 21.4
Post-dose observation period	Day 57	15.7 ± 28.5	-24.2 ± 27.4	5.89 ± 15.5 ^{b)}	-20.4 ± 26.3 ^{b)}

Mean ± SD

a) In patients who shifted to “protocol-off” treatment during the study drug treatment period or the post-dose observation period, missing data were imputed by the “last observation carried forward” (LOCF) method.

b) One patient was excluded from the analysis because the data on Day 57 of the post-dose observation period was missing.

Safety was analyzed. Adverse events¹⁶ occurred in 10 of 12 patients (83.3%) in the placebo group and in 10 of 10 patients (100.0%) in the HNIG group. Table 6 shows adverse events reported by ≥2 patients in either group. Adverse events for which a causal relationship with the study drug could not be ruled out (i.e., adverse drug reactions) were noted in 5 of 12 patients (41.7%) in the placebo group and in 6 of 10 patients (60.0%) in the HNIG group. The adverse drug reaction reported by ≥2 patients in either group was “platelet count decreased” in the HNIG group (20.0% [2 of 10 patients]).

Table 6. Adverse events reported by ≥2 patients in either group

Adverse events	Placebo (n = 12)		HNIG (n = 10)	
	Incidence	No. of patients	Incidence	No. of patients
Total	83.3%	10	100.0%	10
Nasopharyngitis	8.3%	1	30.0%	3
Pemphigoid	25.0%	3	20.0%	2
Diarrhoea	16.7%	2	20.0%	2
Hypokalaemia	8.3%	1	20.0%	2
Dizziness	8.3%	1	20.0%	2
Pyrexia	8.3%	1	20.0%	2
Platelet count decreased	8.3%	1	20.0%	2
Constipation	0%	0	20.0%	2
Hepatic function abnormal	0%	0	20.0%	2
Back pain	0%	0	20.0%	2
Hyperlipidaemia	33.3%	4	10.0%	1
Cushingoid	25.0%	3	10.0%	1
Diabetes mellitus	16.7%	2	10.0%	1
Urine abnormality	16.7%	2	10.0%	1
Malaise	16.7%	2	10.0%	1
Excoriation	16.7%	2	0%	0

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Death (due to aortic rupture) occurred in 1 patient in the HNIG group, but a causal relationship with the study drug was ruled out because it occurred more than 4 months after study drug treatment. Non-fatal serious adverse events occurred in 2 of 12 patients (16.7%) in the placebo group (coronary artery stenosis and pemphigoid [1 patient each]) and in 5 of 10 patients (50.0%) in the HNIG group (cholecystitis acute, pemphigoid, hyperkalaemia, duodenal ulcer, and compression fracture/nausea/vomiting [1 patient each]), but a causal relationship with the study drug was ruled out for all of them. There were no non-fatal adverse events leading to study discontinuation.

3.(ii).A.(2) Japanese phase III study (5.3.5.1-2.1, NPB-01-06/C-01 study [■ 20■ to ■ 20■])

A multi-center, randomized, double-blind, parallel group, placebo-controlled study in patients¹⁷ aged ≥20 years (target sample size, 56) with bullous pemphigoid showing no improvement in clinical

¹⁶ Adverse events observed from Day 1 (the start of study treatment) to Day 169.

¹⁷ Patients with continued treatment of bullous pemphigoid (e.g., corticosteroids including topical drugs, immunosuppressants, tetracycline, minocycline, nicotinamide, diaminodiphenyl sulfone [DDS]) without any addition or change to the therapy after informed consent

symptoms¹⁸ with steroid therapy¹⁹ was conducted in 53 centers in Japan to investigate the efficacy and safety of HNIG.

HNIG (400 mg/kg) or placebo was administered by intravenous infusion once daily for 5 days (study drug treatment period), followed by a post-dose observation period (from the start of administration to Week 8). Plasmapheresis and steroid pulse therapy were prohibited from the beginning of the run-in period (10-21 days) through the end of the post-dose observation period, but were allowed after “protocol-off.”¹⁵

A total of 56 patients were treated (27 in the placebo group, 29 in the HNIG group) and all of them were included in FAS and in the safety analysis set. The FAS was subjected to efficacy analysis. A total of 15 patients discontinued the study (6 in the placebo group, 9 in the HNIG group). The reasons for discontinuation were “decision of the investigator, etc.” (5 patients [2 in the placebo group, 3 in the HNIG group]), “adverse events” (4 patients [2 in the placebo group, 2 in the HNIG group]), “measured IgG, total protein, or A/G ratio in the hospital, which was prohibited to maintain the blindness of the study” (3 patients [1 in the placebo group, 2 in the HNIG group]), “use of prohibited concomitant drugs” (1 patient [1 in the placebo group]), “use of prohibited concomitant therapy” (1 patient [1 in the HNIG group]), and “although symptoms did not meet the criteria for aggravation or no change, the investigator considered that enhanced treatment was necessary” (1 patient [1 in the HNIG group]).

Efficacy was evaluated. Table 7 shows the results of the primary endpoint “PDAI score on Day 15 in the post-dose observation period,” indicating no statistically significant difference between the HNIG group and the placebo group ($P = 0.089$, two-sided significance level 5%, unpaired t test).

Table 7. PDAI score on Day 15 of post-dosing observation period (FAS)

	Placebo (n = 27)	HNIG(n = 29)	P value ^{b)}
Day 1 (the study drug treatment period)	46.3 ± 26.5	46.6 ± 28.2	-
Day 15 (the post-dose observation period) ^{a)}	32.3 ± 31.5	19.8 ± 22.2	$P = 0.089$

Mean ± SD

a) In patients who discontinued or shifted to “protocol-off” treatment during the study drug treatment period or the post-dose observation period, missing data were imputed by the LOCF method.

b) Two-sided significance level, 5%; unpaired t test

Safety was analyzed. Adverse events²⁰ occurred in 24 of 27 patients (88.9%) in the placebo group and in 25 of 29 patients (86.2%) in the HNIG group. Adverse drug reactions were noted in 5 of 27 patients (18.5%) in the placebo group and in 11 of 29 patients (37.9%) in the HNIG group. Adverse events and adverse drug reactions reported by ≥ 2 patients in either group are shown in Tables 8 and 9.

¹⁸ Patients meeting both of the following criteria in terms of the PDAI score (Table 4):

- PDAI score of ≥ 10 on Day 1 of the run-in period
- (i) PDAI score on the last day (Day 10-21) did not improve from the score on Day 1 of the run-in period, (ii) PDAI score increased by ≥ 10 points from the score on Day 1 at ≥ 7 days after the pre-dosing observation period, or (iii) the total clinical symptom score (Table 3) increased by ≥ 2 points from the score on Day 1 at ≥ 7 days after the pre-dosing observation period (if the score on day 1 was ≥ 3 , an increase in the observed value was considered as 1 point increase in score).

¹⁹ Administration of ≥ 0.4 mg/kg/day as prednisolone

²⁰ Adverse events noted between the beginning of the study drug treatment and Day 57

Table 8. Adverse events reported by ≥ 2 patients in either group

Adverse events	Placebo (n = 27)		HNIG(n = 29)	
	Incidence	No. of patients	Incidence	No. of patients
Total	88.9%	24	86.2%	25
Pemphigoid	37.0%	10	17.2%	5
Hypoglycaemia	7.4%	2	13.8%	4
Liver disorder	3.7%	1	13.8%	4
Hypertension	11.1%	3	10.3%	3
Constipation	11.1%	3	10.3%	3
Pyrexia	0%	0	10.3%	3
Blood lactate dehydrogenase increased	0%	0	10.3%	3
Platelet count decreased	0%	0	10.3%	3
Oral candidiasis	18.5%	5	6.9%	2
Nasopharyngitis	7.4%	2	6.9%	2
Diarrhoea	3.7%	1	6.9%	2
Hepatic function abnormal	3.7%	1	6.9%	2
Excoriation	3.7%	1	6.9%	2
Blood pressure increased	3.7%	1	6.9%	2
Conjunctival haemorrhage	0%	0	6.9%	2
Decubitus ulcer	14.8%	4	0%	0
Cytomegalovirus infection	7.4%	2	3.4%	1
Diabetes mellitus	7.4%	2	3.4%	1
Hyponatraemia	7.4%	2	3.4%	1
Insomnia	7.4%	2	0%	0
Haemorrhoids	7.4%	2	0%	0
Arthralgia	7.4%	2	0%	0

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Table 9. Adverse drug reactions reported by ≥ 2 patients in either group

Adverse drug reactions	Placebo (n = 27)		HNIG (n = 29)	
	Incidence	No. of patients	Incidence	No. of patients
Total	18.5%	5	37.9%	11
Liver disorder	3.7%	1	10.3%	3
Platelet count decreased	0%	0	10.3%	3
Hepatic function abnormal	0%	0	6.9%	2
Pyrexia	0%	0	6.9%	2
Blood lactate dehydrogenase increased	0%	0	6.9%	2

MedDRA/J ver14.1

Death occurred in 1 patient in the HNIG group (pneumocystis jiroveci pneumonia²¹), but its causal relationship with the study drug was ruled out. Non-fatal serious adverse events were noted in 2 of 27 patients (7.4%) in the placebo group (toxic epidermal necrolysis and ventricular tachycardia/pneumatosis intestinalis [1 patient each]) and in 1 of 29 patients (3.4%) in the HNIG group (enterocolitis), but a causal relationship with the study drug was ruled out for all of them. Non-fatal adverse events leading to study discontinuation were noted in 2 of 27 patients (7.4%) in the placebo group and in 1 of 29 patients (3.4%) in the HNIG group.²²

²¹ The patient experienced pneumocystis jiroveci pneumonia on 8th day after the completion of HNIG administration and died of MRSA-induced bacterial pneumonia and sepsis on 35th day after the onset of the first adverse event. This patient had been receiving steroid therapy to treat the primary disease, and pneumocystis jiroveci pneumonia was considered to be an opportunistic infection caused by long-term use of corticosteroid.

²² Psychotic disorder and toxic epidermal necrolysis (1 patient each) in the placebo group and neutrophil count decreased (1 patient) in the HNIG group

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

3.(ii).B.(1) Clinical positioning

The applicant's explanation on the clinical positioning of HNIG:

Japanese and foreign guidelines and textbooks (Table 10) recommend high-dose intravenous immunoglobulin (IVIG) therapy for patients with severe bullous pemphigoid inadequately responsive to corticosteroids or are unable to use corticosteroids because of adverse drug reactions.

Table 10. Descriptions on use of immunoglobulin preparations in patients with bullous pemphigoid

Guideline (Japan)
Clinical Practice Guideline 2008. The survey on rare and intractable diseases. General Partial Research Report FY 2007. Integrated Research Report FY 2005 to 2007, attached document 1. March 2008, p.15-33 Bullous pemphigoid is treated mainly with oral corticosteroid. For intractable cases, steroid pulse therapy, immunosuppressants, plasmapheresis, IVIG therapy, or interferon gamma therapy in combination with corticosteroids are recommended. Concomitant use of IVIG therapy is useful for severe cases non-responsive to oral corticosteroids and immunosuppressants (recommendation class C1: The use of this therapy may be considered but lacks sufficient evidence).
Guidelines (foreign countries)
European Dermatology Forum Guideline Subcommittee. Guidelines on the use of high-dose intravenous immunoglobulin in dermatology (<i>Eur J Dermatol.</i> 2009;19:90-98) Immunoglobulin therapy may be indicated for severe bullous pemphigoid (evidence level III, recommendation class B). Administer 2 g/kg in divided doses over 2 to 5 days as an additional treatment when existing treatments are not effective.
British Association of dermatologists' guidelines for the management of bullous pemphigoid 2012 (<i>Br J Dermatol.</i> 2012;167:1200-1214) This guideline presents a small retrospective survey and case reports on a total of 41 patients treated with immunoglobulin preparations. Administer 2 g/kg in divided doses over 3 days to patients with severe bullous pemphigoid inadequately responsive to corticosteroids and immunomodulators (evidence level III [case reports, etc.], recommendation class D [presumptions from studies with levels of evidence 3, 4, and 2+, or official consensus]).
National Blood Authority. Criteria for the clinical use of intravenous immunoglobulin in Australia. 2nd ed. 2012 Immunoglobulin therapy is indicated for patients with bullous pemphigoid refractory to corticosteroids and immunosuppressive therapy (insufficient data with category-4a small-scale studies only). Treatment with 2 g/kg in 1-month cycles is effective.
Canadian consensus statement on the use of intravenous immunoglobulin therapy in dermatology (<i>J Cutan Med Surg.</i> 2006;10:205-221) Immunoglobulin therapy was effective when administered at a dose of 2g/kg/cycle to 15 patients with bullous pemphigoid who had experienced severe adverse reactions to conventional treatments. Together with the above report, results of a study in 10 patients with severe bullous pemphigoid treated with a immunoglobulin preparation provide limited evidence supporting the use of immunoglobulin therapy in patients who are non-responsive to, or contraindicated for, conventional treatments (evidence level 4).
Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases (<i>Arch Dermatol.</i> 2003;139:1051-1059) According to 5 sources of English literature, immunoglobulin therapy was effective in 27 out of 32 patients with bullous pemphigoid unresponsive to conventional treatments such as corticosteroids, with only a few adverse drug reactions.
Textbook (available in Japan)
Standard Textbook of Dermatology. 10th ed. Igaku Shoin Ltd.;2013:241-243 Steroid pulse therapy, immunosuppressants, plasmapheresis, and IVIG therapy are administered in combination with an immunoglobulin preparation for intractable bullous pemphigoid.
Textbook (available in foreign countries)
Fitzpatrick's dermatology in general medicine. 8th ed. McGraw Hill Medical;2012:608-616 This textbook carries small scale study reports claiming that plasmapheresis, IVIG therapy, methotrexate, leflunomide, and chlorambucil are effective.

“A survey on a high-dose intravenous immunoglobulin therapy for bullous pemphigoid²³” was conducted in Japan. Of 96 medical institutions that responded to the questionnaire, 95 (99.0%) replied that IVIG therapy is necessary as a therapeutic option. The survey collected information on the efficacy and safety of IVIG therapy in 90 patients. According to the information, the therapy was “very effective” in 28 of 90 patients (31.1%), “effective” in 42 of 90 patients (46.7%), “slightly effective” in 13 of 90 patients (14.4%), and “ineffective” in 7 of 90 patients (7.8%) and, as for the safety, adverse drug reactions did not occur in 83 of 90 patients (92.2%) and occurred in 7 of 90 patients (7.8%).

PMDA's view:

Both in Japan and in foreign countries, IVIG therapy is positioned as a therapeutic option for patients with bullous pemphigoid inadequately responsive to other therapies such as corticosteroids, and there is

²³ *Journal of new remedies & clinics.* 2014;63:50-59

some experience with IVIG therapy in Japan. Taking account of the results of the phase III study, PMDA considers that HNIG can be a therapeutic option for patients with bullous pemphigoid who have aggravated symptoms and are inadequately responsive to corticosteroids.

3.(ii).B.(2) Efficacy

Although the phase III study did not demonstrate the superiority of HNIG to placebo in the primary endpoint “PDAI score on Day 15 in the post-dosing observation period,” the review in 3.(ii).B.(2).1) to 3.(ii).B.(2).3) below revealed that the PDAI score, erosion/blisters and erythema, as well as clinical symptoms tended to improve with the administration of HNIG. PMDA therefore considers that the efficacy of HNIG has been demonstrated.

The decision on the efficacy of HNIG will be finalized, based on the comments raised in the Expert Discussion.

3.(ii).B.(2).1) Primary endpoint of the phase III study

The applicant’s explanation on the justification for setting the primary endpoint of the phase III study as “PDAI score on Day 15 in the post-dosing observation period” and the results:

Since there are no established criteria to assess the drug efficacy in the treatment of bullous pemphigoid, the applicant investigated the feasibility of using PDAI for efficacy evaluation in the clinical study of HNIG. PDAI is an index used internationally to assess the severity of a related disease, pemphigus. In the phase II study, PDAI score tended to be lower in the HNIG group than in the placebo group at many evaluation time points. These results were almost identical with the results such as “total clinical symptom score,” showing no significant discrepancies between the indices. Based on these results, the PDAI score was selected as the primary endpoint in the phase III study. If a therapy shows no efficacy in the treatment of bullous pemphigoid in approximately 2 weeks, usually an additional treatment is given. This indicates the clinical significance of improving clinical symptoms in approximately 2 weeks, thus the applicant decided to evaluate the PDAI score on Day 15 of the post-dose observation period.

Table 7 shows PDAI score on Day 15 in the post-dosing observation period (the primary endpoint) in the phase III study. The results showed no statistically significant difference between the HNIG group and the placebo group. Patients enrolled in the phase III study had more severe bullous pemphigoid (greater PDAI score) than those in the phase II study. As a result, the common standard deviation of PDAI score among treatment groups in the phase III study was greater than that in the phase II study used to calculate the target sample size for the phase III study (27.1 vs. 16.6), resulting in an insufficient statistical power.

Based on the results of the phase III study, the feasibility of an additional clinical study was investigated. The required number of patients calculated from the results of the phase III study was 180. According to the questionnaire responses from medical institutions participating in the study, the number of patients indicated for IVIG therapy in Japan was approximately 600 to 630, accounting for approximately 10% of patients with bullous pemphigoid. Moreover, approximately 200 to 210 patients among them were assumed to meet the inclusion criteria for the phase III study. Since patients treated with the study drug in the phase II or III study are to be excluded from the additional clinical study and only a limited number of clinical institutions can participate, an extremely limited number of patients are eligible for enrollment in the study. Given that the phase III study (56 patients) took ■ years to complete, the applicant considers it practically impossible to conduct an additional clinical study.

The results of the phase III study were subjected to a post hoc covariance analysis using “PDAI score on Day 1 (pre-dose) of the study drug treatment period” as the covariate. The least squares mean of “PDAI score on Day 15 in the post-dose observation period” was as low as 19.7 in the HNIG group, while being 32.4 in the placebo group ($P = 0.041$ in analysis of covariance test).

Figure 1 shows changes over time in PDAI score (observed value)²⁴ in the phase III study. The score in the HNIG group remained lower than that in the placebo group up to Day 57 in the post-dose observation period.

²⁴ Data after study discontinuation or “off-protocol” were imputed with those at time of the discontinuation/“off-protocol” (LOCF).

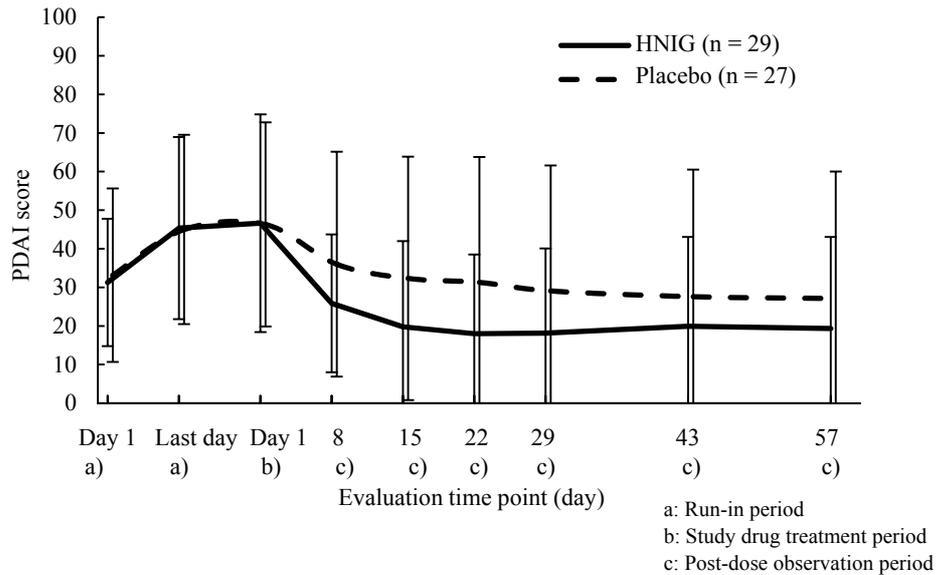


Figure 1. Change in PDAI score (observed value) over time (mean ± SD) (FAS)

Thus, the applicant considers that the results of PDAI score in the phase III study suggest the therapeutic effect of HNIG.

PMDA's view:

Taking account that there is no established criteria to evaluate the drug efficacy for the treatment of bullous pemphigoid, with the results of the phase II study, the use of "PDAI score on Day 15 in the post-dose observation period" as the primary endpoint in the phase III study is acceptable.

Since the superiority of HNIG to placebo was not validated in the primary analysis of "PDAI score on Day 15 in the post-dose observation period" in the phase III study, an additional clinical study is preferably required. However, given the limited number of patients in Japan, it is practically impossible to conduct an additional clinical study.

Although no statistically significant difference was observed between the HNIG group and the placebo group in "PDAI score on Day 15 in the post-dose observation period" in the phase III study, observed PDAI score (Figure 1) in the HNIG group remained lower than that in the placebo group from the beginning of the study drug treatment through Day 57 in the post-dosing observation period, demonstrating that PDAI score tended to be improved by HNIG.

3.(ii).B.(2).2 Main secondary endpoints of the phase III study

(a) Changes in erosion/blister and new erythema over time

Figure 2 shows changes over time in erosion/blister and new erythema, the symptoms that constitute PDAI score (observed value)²⁴. They remained lower in the HNIG group than in the placebo group.

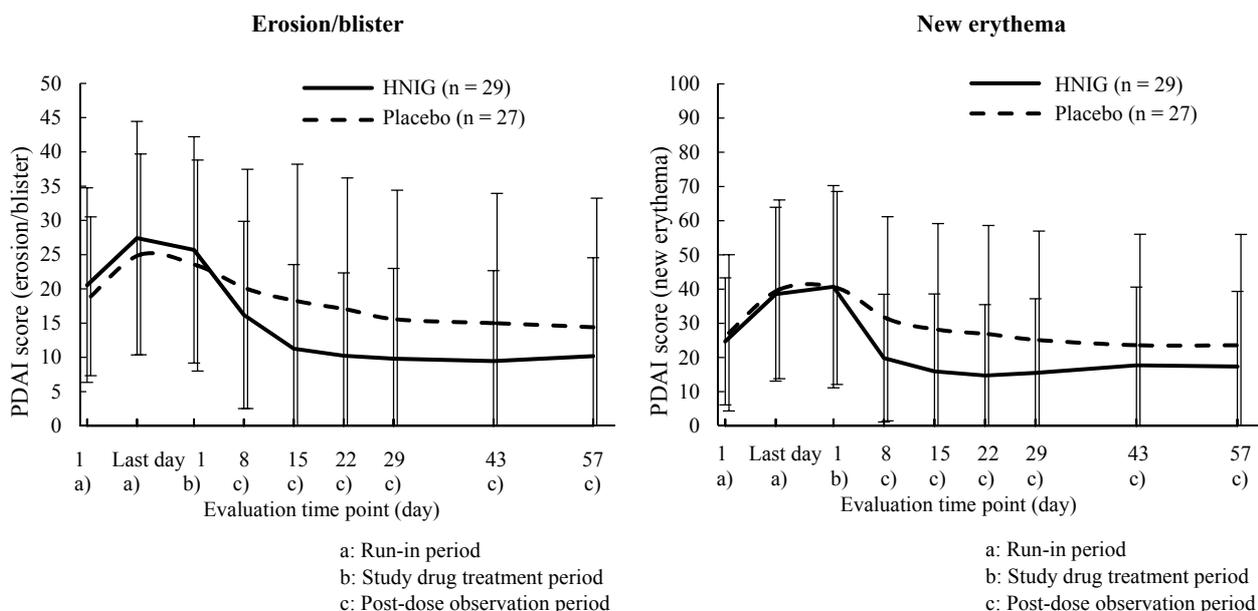


Figure 2. Changes over time in PDAI score (erosion/blister, new erythema) (observed value) (mean \pm SD) (FAS)

(b) Change in clinical symptom score over time

Figure 3 shows the change in the sum of clinical symptom scores (observed value) over time.²⁴ The score remained lower in the HNIG group than in the placebo group.

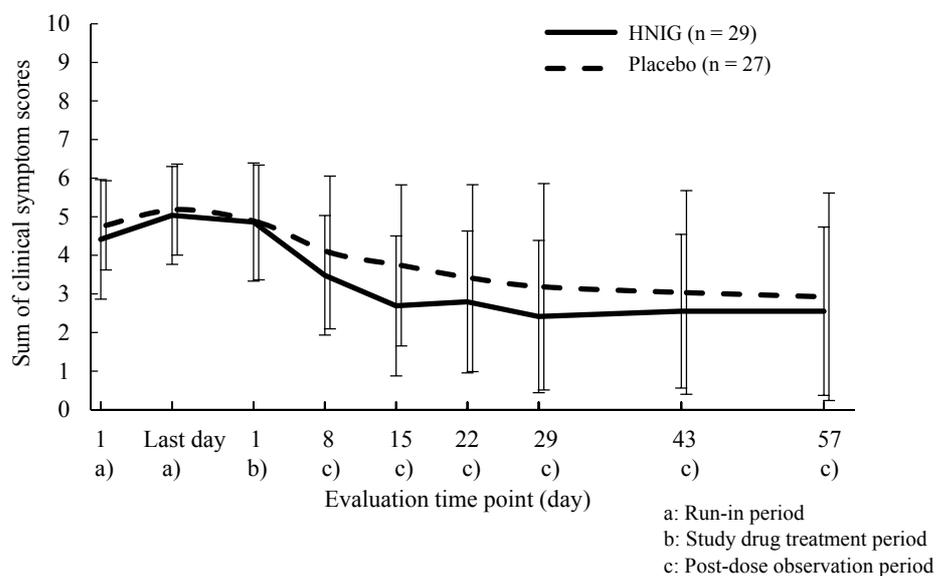


Figure 3. Change in the sum of clinical symptoms scores (observed value) over time (mean \pm SD) (FAS)

PMDA confirmed that “changes over time in erosion/blister and new erythema” and “change over time in the sum of clinical symptom scores,” albeit investigated in an exploratory manner, remained consistently lower in the HNIG group than in the placebo group, in the same way as the PDAI score.

3.(ii).B.(2).3) Efficacy by severity before administration

Table 11 shows the efficacy in patients classified by severity before study drug treatment. In all subpopulations classified by pre-dose PDAI score, “PDAI score on Day 15 in the post-dosing observation period” tended to be lower in the HNIG group than the placebo group. “Clinical symptom

score” showed a similar tendency in both subpopulations (sums of clinical symptom scores of ≤5 and 6 points).

Table 11. PDAI score on Day 15 in the post-dosing observation period by pre-dosing score (FAS)

Score on the last day of the run-in period	Placebo	HNIG	
PDAI score	10-24	12.1 ± 16.8 (n = 8)	5.7 ± 5.7 (n = 7)
	25-39	34.7 ± 38.7 (n = 3)	16.0 ± 10.1 (n = 4)
	40-54	41.1 ± 32.5 (n = 7)	21.0 ± 18.9 (n = 9)
	55-69	32.8 ± 23.2 (n = 5)	23.2 ± 18.6 (n = 5)
	≥70	55.0 ± 46.6 (n = 4)	41.3 ± 43.5 (n = 4)
Sum of clinical symptom scores	≤5	20.8 ± 30.0 (n = 11)	12.3 ± 16.6 (n = 15)
	6	40.3 ± 31.0 (n = 16)	27.9 ± 25.1 (n = 14)

Mean ± SD

PMDA’s view:

Since the scores were lower in the HNIG group than in the placebo group in all subpopulations, albeit each group comprises only a small number of patients, HNIG is expected to be effective in patients with bullous pemphigoid regardless of the severity of the disease.

3.(ii).B.(3) Safety

PMDA’s view:

Based on the review in 3.(ii).B.(3).1 and 3.(ii).B.(3).2) below, there is no significant safety problem in using HNIG for the treatment of bullous pemphigoid and HNIG is clinically acceptable provided that similar safety measures are taken as those in the treatment of pemphigus.

The decision on the safety of HNIG will be finalized, based on the comments raised in the Expert Discussion.

3.(ii).B.(3).1 Incidences of adverse events in clinical studies (pooled analysis)

Table 12 shows the incidences of adverse events in the pooled analysis of the phase II and III study data. The incidence of adverse drug reactions tended to be higher in the HNIG group than in the placebo group, but there was no tendency of causing clinically significant problems. The incidence of serious adverse events was 10.3% (4 of 39 patients) in the placebo group and 17.9% (7 of 39 patients) in the HNIG group, showing that the events occurred more frequently in the HNIG group than in the placebo group. However, a causal relationship with the study drug was ruled out for all the events, and there was no tendency of any specific serious adverse events to occur.

Table 12. Adverse events reported by ≥ 2 patients in either group (pooled data of phase II and III studies)

Adverse events	Placebo (n = 39)		HNIG (n = 39)		Adverse events	Placebo (n = 39)		HNIG (n = 39)	
	Incidence	No. of patient	Incidence	No. of patients		Incidence	No. of patients	Incidence	No. of patients
Total	87.2%	34	89.7%	35	Blood pressure increased	5.1%	2	5.1%	2
Adverse drug reactions	25.6%	10	43.6%	17	Drug eruption	2.6%	1	5.1%	2
Pemphigoid	33.3%	13	17.9%	7	Gamma-glutamyltransferase increased	2.6%	1	5.1%	2
Nasopharyngitis	7.7%	3	12.8%	5	Contusion	2.6%	1	5.1%	2
Constipation	7.7%	3	12.8%	5	Hypoalbuminaemia	0%	0	5.1%	2
Pyrexia	2.6%	1	12.8%	5	Zinc deficiency	0%	0	5.1%	2
Platelet count decreased	2.6%	1	12.8%	5	Conjunctival haemorrhage	0%	0	5.1%	2
Diarrhoea	7.7%	3	10.3%	4	Upper respiratory tract inflammation	0%	0	5.1%	2
Hypoglycaemia	5.1%	2	10.3%	4	Toxic skin eruption	0%	0	5.1%	2
Hepatic function abnormal	2.6%	1	10.3%	4	Back pain	0%	0	5.1%	2
Liver disorder	2.6%	1	10.3%	4	Lymphocyte count decreased	0%	0	5.1%	2
Oral candidiasis	15.4%	6	7.7%	3	Hyponatraemia	7.7%	3	2.6%	1
Hypertension	10.3%	4	7.7%	3	Insomnia	5.1%	2	2.6%	1
Hypokalaemia	2.6%	1	7.7%	3	Vomiting	5.1%	2	2.6%	1
Blood lactate dehydrogenase increased	0%	0	7.7%	3	Arthralgia	5.1%	2	2.6%	1
Cushingoid	10.3%	4	5.1%	2	Urine abnormality	5.1%	2	2.6%	1
Diabetes mellitus	10.3%	4	5.1%	2	Decubitus ulcer	10.3%	4	0%	0
Hyperlipidaemia	10.3%	4	5.1%	2	Laceration	7.7%	3	0%	0
Excoriation	7.7%	3	5.1%	2	Haemorrhoids	5.1%	2	0%	0
Cytomegalovirus infection	5.1%	2	5.1%	2	Dermatitis	5.1%	2	0%	0
Dizziness	5.1%	2	5.1%	2	Glucose urine present	5.1%	2	0%	0
Malaise	5.1%	2	5.1%	2	White blood cell count increased	5.1%	2	0%	0

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3.(ii).B.(3).2 Comparison with approved indications

The applicant's explanation on the safety profile of HNIG in the treatment of bullous pemphigoid:

The incidences of adverse events in Japanese clinical studies were compared between those in the treatment of bullous pemphigoid and those in the treatment of pemphigus, a related disease among the approved indications of HNIG. In the Japanese clinical study involving patients with pemphigus,²⁵ the incidence of adverse event was 82.9% (34 of 41 patients), and adverse events with an incidence of $\geq 10\%$ were nasopharyngitis (19.5% [8 of 41 patients]), alanine aminotransferase increased (17.1% [7 of 41 patients]), and pemphigus (12.2% [5 of 41 patients]). The incidences of adverse events in Japanese clinical studies involving patients with bullous pemphigoid are shown in Table 12, indicating no significant difference between the profile of adverse events and the profile observed in the study in patients with pemphigus. Both are autoimmunity-related diseases and are treated mainly with corticosteroids and immunosuppressants, suggesting that there will be no significant difference between the two diseases in terms of the profile of adverse events associated with the concomitant use of HNIG with existing therapies.

Moreover, since the adverse drug reactions observed in the submitted phase II and III study data are generally known to occur with approved indications, currently there are no particular safety problems that require any actions in using HNIG for the treatment of bullous pemphigoid.

PMDA's view:

Although only a limited number of patients were investigated in the clinical studies, the safety profile of HNIG in patients with bullous pemphigoid does not show any clinically significant difference from the profile in patients with pemphigus. The safety profile of HNIG used for the treatment of bullous

²⁵ Combined analysis data of 200 mg/kg group (n = 20) and 400 mg/kg group (n = 21)

pemphigoid is therefore tolerable provided that similar safety measures are taken as those in the treatment of pemphigus.

Since HNIG is manufactured from human blood, the risk of infection with unknown viruses cannot be completely excluded. Use of HNIG should be limited to the minimum necessary for treatment and its therapeutic necessity should be thoroughly considered prior to use.

3.(ii).B.(4) Indication

Results of the phase III study in patients with bullous pemphigoid inadequately responsive to steroid therapy suggest the efficacy of HNIG with a well-tolerated safety profile. In addition, there is some experience with IVIG therapy in patients with bullous pemphigoid inadequately responsive to steroid therapy, both in Japan and foreign countries. Taking account of the above, PMDA considers that the proposed indication of “bullous pemphigoid (for patients with BP inadequately responsive to corticosteroids)” for HNIG should be acceptable.

3.(ii).B.(5) Dosage and administration

The applicant’s explanation on the justification for the dosage and administration of HNIG: According to the Consensus Statement of the US,²⁶ IVIG therapy is expected to be effective for the treatment of bullous pemphigoid if administered at 2 g/kg per cycle. In the clinical study in patients with pemphigus, HNIG 400 mg/kg/day for 5 consecutive days was demonstrated to be effective. Although the autoantibody causing bullous pemphigoid is different from that of pemphigus, both diseases are autoimmune bullous in which binding of an autoantibody to an epidermal component, the antigen, triggers blister formation. Therefore, the dosage regimen of HNIG 400 mg/kg/day for 5 consecutive days was used in the phase II study. Results of the phase II study suggested the efficacy of HNIG 400 mg/kg/day administered for 5 consecutive days, with a similar safety profile as that observed for the approved indications. Based on these results, the same dosage regimen was employed in the phase III study. Results of the phase III study suggested that HNIG 400 mg/kg/day for 5 consecutive days was effective and showed that the safety profile was not significantly different from that observed for the approved indications, with no serious adverse drug reactions. The applicant therefore considered that there were no new safety concerns.

PMDA’s view:

In the phase III study, the applicant decided to set the dosage and administration of HNIG at 400 mg/kg/day for 5 consecutive days by referring to the approved dosage and administration for pemphigus and to published literature. The decision is acceptable. Results of the phase III study suggested the efficacy of HNIG without any safety problems. Therefore, there are no particular problems in setting the dosage and administration as that used in the phase III study for patients with bullous pemphigoid inadequately responsive to corticosteroids.

3.(ii).B.(6) Post-marketing investigations

Judging from the results of the clinical studies of HNIG and other findings, there appears no new safety concerns in the risk management plan pertaining to this application. No additional pharmacovigilance activities or risk minimization activities are necessary at this point.

III. Results of Compliance Assessment Concerning the Data Submitted in the 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 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 for the data submitted in the application. PMDA thus concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

²⁶ *Arch Dermatol.* 2003;139:1051-1059

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

GCP on-site inspection 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 for the data submitted in the application (5.3.5.1-1, 5.3.5.1-2.1). PMDA 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 HNIG in the treatment of patients with bullous pemphigoid inadequately responsive to corticosteroids has been demonstrated and its safety is acceptable in view of its observed benefits. HNIG provides a therapeutic option for patients with bullous pemphigoid inadequately responsive to corticosteroids, and is thus of clinical significance. This application can be approved if HNIG is not considered to have any particular problems with the efficacy, safety, indication, and dosage and administration based on comments from the Expert Discussion.

Review Report (2)

October 9, 2015

I. Product Submitted for Registration

[Brand name]	Kenketu Glovenin-I for I.V. Injection 500 mg, Kenketu Glovenin-I for I.V. Injection 2500 mg, Kenketu Glovenin-I for I.V. Injection 5000 mg
[Non-proprietary name]	Freeze-dried Polyethylene Glycol Treated Human Normal Immunoglobulin
[Applicant]	Nihon Pharmaceutical Co., Ltd.
[Date of application]	December 25, 2014

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).

(1) Efficacy and clinical positioning

PMDA’s view:

In the phase III study (Study NPB-01-06/C-01) in patients with bullous pemphigoid who did not show improvement in clinical symptoms with steroid therapy, no statistically significant difference was observed in the primary endpoint, “PDAI score on Day 15 in the post-dosing observation period,” between the HNIG group and the placebo group. Since superiority of the HNIG group to the placebo group was not validated in this study, an additional clinical study is preferably required. However, such an additional study was practically impossible because the number of patients with bullous pemphigoid who would be eligible for treatment with HNIG is limited in Japan.

In the phase III study, PDAI score (observed value) remained consistently lower in the HNIG group than in the placebo group throughout the period from the beginning of the study drug treatment through Day 57 in the post-dose observation period, showing a tendency of improvement in the PDAI score by the administration of HNIG. Erosion/blister and erythema as well as clinical symptoms also tended to improve.

Based on the above, PMDA has concluded that the efficacy of HNIG in patients with bullous pemphigoid inadequately responsive to corticosteroids is demonstrated.

In Japanese and foreign guidelines, etc., high-dose intravenous immunoglobulin (IVIG) therapy is positioned as a therapeutic option for patients with bullous pemphigoid inadequately responsive to corticosteroids, and there is of some experience with IVIG therapy in Japan as well as in other countries. Given the results of the phase III study and the positioning of IVIG therapy in the treatment of bullous pemphigoid, HNIG serves as a therapeutic option for patients with bullous pemphigoid who have aggravated symptoms and are inadequately responsive to corticosteroids.

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

(2) Safety

PMDA’s view:

Although only a limited number of patients were investigated in the clinical studies, the safety profile of HNIG in patients with bullous pemphigoid does not show any clinically significant difference from the profile in patients with pemphigus, and most of the adverse drug reactions observed in the phase II

and III studies are known events. Based on the above, the safety profile of HNIG in the treatment of bullous pemphigoid is tolerable provided that similar safety measures are taken as those in the treatment of pemphigus.

Since HNIG is manufactured from human blood, the risk of infection with unknown viruses cannot be completely excluded. Therefore, the use of HNIG should be limited to the minimum necessary for treatment and its therapeutic necessity should be thoroughly considered prior to use.

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

(3) Indication

Based on the results of the review of the efficacy and safety, and taking account that in and outside Japan there is some experience with IVIG therapy in patients with bullous pemphigoid inadequately responsive to corticosteroids, PMDA has concluded that there should be no problem to add “bullous pemphigoid (for patients with BP inadequately responsive to corticosteroids)” in the indications of HNIG.

The above conclusions of the PMDA were supported by the expert advisors at the Expert Discussion. Therefore, PMDA has concluded that “Indication” and “Precautions for Indications” should be as follows:

[Indication]

Bullous pemphigoid (for patients with BP inadequately responsive to corticosteroids)
(Newly added indication only)

[Precautions for Indications]

For the treatment of bullous pemphigoid, HNIG should be used only in patients inadequately responsive to appropriate treatment with corticosteroids. In clinical studies, the efficacy and safety of HNIG were investigated in patients who did not show improvement in clinical symptoms after treatment with corticosteroid ≥ 0.4 mg/kg/day (prednisolone-equivalent dose) for 7 to 21 days.
(Newly added precautions only)

(4) Dosage and administration

Based on the review of the efficacy and safety, PMDA considered that there should be no particular problem in setting the dosage and administration for patients with bullous pemphigoid inadequately responsive to corticosteroids as that used in the phase III study.

The above conclusions of the PMDA were supported by the expert advisors. Also, the following comment was raised from the expert advisors regarding the necessity of multiple-dose administration of HNIG in patients with bullous pemphigoid (for patients with BP inadequately responsive to corticosteroids):

- Since HNIG is a symptomatic treatment for bullous pemphigoid, recurrence/relapse of symptoms may occur after remission. When symptoms have aggravated again after improvement with HNIG, additional use of HNIG in the patient after thorough consideration of the necessity of the treatment is presumable. However, since unnecessarily continuous use of HNIG should be avoided and since the foreign guideline recommends a treatment cycle of approximately 1 month,²⁷ caution should be provided not to give additional doses within approximately 1 month after the administration of HNIG, in the same way as in the treatment of the related disease pemphigus.

Based on the above, PMDA instructed the applicant to revise the “Dosage and Administration” and “Precautions for Dosage and Administration” as shown below. The applicant took appropriate measures and PMDA accepted the applicant’s response.

²⁷ *Arch Dermatol.* 2003;139:1051-1059, *Br J Dermatol.* 2012;167:1200-1214, *Eur J Dermatol.* 2009;19:90-98, etc.

[Dosage and Administration]

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

[Precautions for Dosage and Administration]

Improvement in symptoms of pemphigus and of bullous pemphigoid may be observed within 4 weeks after the completion of treatment with HNIG. Patients should be carefully monitored after the treatment, and HNIG should not be administered additionally for 4 weeks after the completion of treatment with HNIG.

(Newly added dosage and administration only; additions underlined in precautions)

III. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved for the indications and dosage and administration as shown below:

[Indications]

1. Agammaglobulinemia or hypogammaglobulinemia
2. Coadministration with antibiotics for the treatment of severe infection
3. Idiopathic thrombocytopenic purpura (ITP) (for patients with ITP unresponsive to other drugs who have a marked bleeding tendency and who require temporary hemostasis during emergency procedures including surgery and delivery)
4. Kawasaki disease (KD) in the acute phase (for patients with severe KD who have a risk of coronary artery disorder)
5. Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)
6. Pemphigus (for patients with pemphigus inadequately responsive to corticosteroids)
7. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (for patients with SJS or TEN inadequately responsive to corticosteroids)
8. Bullous pemphigoid (BP) (for patients with BP inadequately responsive to corticosteroids)

(Underline denotes additions.)

[Dosage and administration]

The product 500 mg should be reconstituted with 10 mL of the supplied solvent (Water for Injection [the Japanese Pharmacopoeia]). The reconstituted solution should be administered according to the regimens specified below for each indication. Direct intravenous injection should be given at a very slow rate.

Agammaglobulinemia or hypogammaglobulinemia:

The usual dosage of human immunoglobulin G is 200 to 600 mg (in 4-12 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection once every 3 to 4 weeks. The dose may be adjusted according to the patient's condition.

Coadministration with antibiotics for the treatment of severe infection:

The usual single dosage of human immunoglobulin G is 2500 to 5000 mg (in 50-100 mL) for adults, and 100 to 150 mg (in 2-3 mL)/kg body weight for children, administered by an intravenous infusion or a direct intravenous injection. The dose may be adjusted according to the patient's condition.

Idiopathic thrombocytopenic purpura:

The usual daily dosage of human immunoglobulin G is 200 to 400 mg (in 4-8 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection. If symptoms do not improve after 5-day intravenous immunoglobulin treatment, the treatment should be discontinued. The dose may be adjusted according to the patient's age and condition.

Kawasaki disease in the acute phase:

The usual dosage of human immunoglobulin G is 200 mg (in 4 mL)/kg body weight administered once daily for 5 days by an intravenous infusion or a direct intravenous injection, or 2000 mg (in 40 mL)/kg body weight administered by a single intravenous infusion. The dose for 5-day administration may be decreased or increased according to the patient's age and condition, and the dose for single-dose administration may be decreased according to the patient's age and condition.

Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy):

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion or a direct intravenous injection. The dose may be decreased according to the patient's age and condition.

Pemphigus:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion. The dose may be decreased according to the patient's age and condition.

Stevens-Johnson syndrome and toxic epidermal necrolysis:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by a drip intravenous infusion.

Bullous pemphigoid:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

(Underline denotes additions.)