This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Investigation Result Report

May 22, 2020
Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Nonproprietary name]	Not applicable to combination drugs
[Brand name]	See Appendix 1
[Authorization holder]	See Appendix 1
[Indications]	See Appendix 1
[Dosage and administration]	See Appendix 1
[Remarks]	Nothing noteworthy
[Investigating office]	Office of Pharmacovigilance I

II. Backgrounds for this investigation

Parenteral nutrition preparations widely used to supplement water, electrolyte, amino acid under malnutrition or before/after surgery (divided into amino-acid preparations, peripheral parenteral nutrition (hereinafter referred to as “PPN”) preparations, and total parenteral nutrition (hereinafter referred to as “TPN”) preparations) are contraindicated in “patients with serious renal disorder” and “patients with azotaemia.” In addition, PPN preparations and TPN preparations are contraindicated in “patients with oliguria.” The rationale for the above contraindication for each parenteral nutrition preparation is as follows:

- Amino acid preparations contain amino acid. The preparations are contraindicated in “patients with serious renal disorder or patients with azotaemia” for the reason that urea, a metabolite of amino acid, remains for a long time, possibly leading to aggravation of the symptom, etc.
- PPN preparations contain amino acid, glucose, electrolyte, etc. The preparations are contraindicated in “patients with serious renal disorder or patients with azotaemia” for the reason that excessive water/electrolyte consumption or accumulated urea may aggravate the symptom, etc. They are also contraindicated in “patients with oliguria” for the reason that hyperkalaemia can be aggravated or induced.
- TPN preparations are divided into a basic solution and kit agent. Basic solution contains glucose, electrolyte, etc. The solution is used after being mixed with an amino acid preparation. Kit agent contains multivitamin, trace element, fat emulsion, etc. in addition to amino acid, glucose, and electrolyte. Any of these preparations is contraindicated in “patients with serious renal disorder,” “patients with azotaemia,” and “patients with oliguria” for the same reason as PPN preparations.

Amino acid preparations for renal failure and TPN basic solution for renal failure are marketed

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as a parenteral nutrition preparation used in patients with serious renal disorder including those on dialysis or hemofiltration in Japan. The issues that should be addressed are as follows:

- As the concentration of amino acid preparations for renal failure is lower than that of regular amino acid preparations, administration of the required volume of protein will result in heavier fluid overloads[1].
- Considering the excretory disorder of electrolyte associated with renal failure, TPN's basic solution for renal failure does not contain potassium and phosphorus. The solution contains the minimal level of various electrolytes (sodium, magnesium, calcium, chloride, and zinc) to be used with necessary electrolytes replenished[2]. Aseptic control of infusion solution is essential to implement TPN. Since there is a strong correlation between the number of operation processes and opportunities for accidents or infections, it is important to minimize the number of drugs mixed with TPN agent[3].

In June 2017, the Japanese Society for Parenteral and Enteral Nutrition (the Japanese Society for Clinical Nutrition and Metabolism, at present) submitted "Request for review of the package insert language concerning contraindications for parenteral nutrition preparations" to the Pharmaceutical Safety and Environmental Health Bureau (hereinafter referred to as "PSEHB") of the Ministry of Health, Labour and Welfare (hereinafter referred to as "MHLW") and Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"). The request focused on revision of the package insert to exclude patients on dialysis or on hemofiltration from the "patients with serious renal disorder" in the Contraindications section mainly for the following reasons:

- Dialysis or hemofiltration removes low-molecular substances such as water, electrolyte, amino acid, etc. as well as uraemia substances in patients on these procedures.
- As the conditions of patients on dialysis or hemofiltration vary, multiple options for nutrition management are necessary.
- A guideline issued by the European Society for Clinical Nutrition and Metabolism (hereinafter referred to as "ESPEN") says that administration of standard preparations[4] is appropriate to most patients on dialysis with chronic kidney disease and also with some acute diseases when they receive parenteral nutrition therapy.

Moreover, the Japanese Society of Intensive Care Medicine also submitted a request with the same contents as the above to the PSEHB of MHLW in November 2017.

The Pharmaceutical Safety Division, PSEHB of MHLW asked PMDA on March 5, 2020 to conduct an investigation on the safety of parenteral nutrition preparations in patients with serious renal disorder on dialysis or hemofiltration. The Division also asked PMDA to conduct an

[1] Hamada Yasuhiro, the Journal of Japanese Society for Parenteral and Enteral Nutrition. 2018; 33: 848-52

[2] Hicaliq RF Infusion solution Interview Form Version 6 (revised April 2019)

[3] Guideline for parenteral and enteral nutrition Version 3. Japanese Society for Parenteral and Enteral Nutrition, 2013:84-6

[4] Preparations that are not condition-specific ones

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investigation on amino acid preparations for hepatic failure as drugs to investigate in addition to parenteral nutrition preparations because amino acid preparations for hepatic failure were intravenous preparations containing amino acid, and contraindicated in "patients with serious renal disorder" based on the same rationale as parenteral nutrition preparations, although amino acid preparations do not aim to control nutrition. PMDA conducted an investigation based on the request and discussed the necessity of revision in the package insert.

PMDA held an Expert Discussion as part of the investigation. The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the "Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Investigation at PMDA

1. Volume of water, electrolyte, and urea removed by dialysis or hemofiltration

The excess of water and electrolyte, as well as accumulation of urea, are mentioned as the rationale for contraindication in "patients with serious renal disorder." Blood purifier (hollow fiber type) function category 2013 (Journal of Japanese Society for Dialysis Therapy. 2013; 46: 501-6.) shows urea clearance by a blood purifier. It is determined to be ≥125 mL/min or ≥185 mL/min by hemodialyzer, depending on the type[5], ≥200 mL/min[6] for post dilution and ≥180 mL/min[7] for pre-dilution by hemodiafiltration machine, and ≥55 mL/min[8] by hemofiltration machine.

2. Japanese and overseas guidelines, etc.

PMDA investigated the relevant guidelines on nutrition control in patients with chronic kidney disease including those on dialysis or hemofiltration or patients with acute kidney injury. PMDA also investigated the relevant guidelines on administration of amino acid preparations for hepatic failure for hepatic encephalopathy in patients on dialysis or hemofiltration.

1) Dietary recommendations for chronic kidney disease, 2014 (Japanese Journal of Nephrology. 2014; 56: 553-99)

For nutrition control for patients with chronic kidney disease (hereinafter referred to as "CKD"), the recommended intake of energy, protein, salt, potassium, etc. is specified, depending on the level of glomerular filtration rate (hereinafter referred to as "GFR"). The recommended protein intake for Stage 1 to 5 is reduced as GFR decreases (Table 1). On the other hand, the recommended protein intake for Stage 5D is 0.9 to 1.2 g/kgBW/day in patients on hemodialysis

[5] Measurement condition: membrane area, 1.5 m^2; blood flow, 200 ± 4 mL/min, dialysate flow, 500 ± 15 mL/min; filtration flow/replenisher solution flow, 15 ± 1 mL/min (10 ± 1 mL/min/m^2)
[6] Measurement condition: membrane area, 2.0 m^2; blood flow, 250 ± 5 mL/min, dialysate flow, 500 ± 15 mL/min; filtration flow/replenisher solution flow, 60 ± 2 mL/min (30 ± 1 mL/min/m^2)
[7] Measurement condition: membrane area 2.0 m^2; blood flow, 250 ± 5 mL/min; post dilution, 490 ± 10 mL/min; dialysate flow, 600 ± 18 mL/min; inflow, 360 ± 11 mL/min; filtration flow/replenisher solution flow, 240 ± 4 mL/min (120 ± 2 mL/min/m^2)
[8] Measurement condition: membrane area 2.0 m^2; blood flow, 250 ± 5 mL/min; filtration flow/replenisher solution flow, 60 ± 2 mL/min (30 ± 1 mL/min/m^2)

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and peritoneal dialysis (Table 2), that is, a higher protein intake is recommended than that for Stage 3a.

Table 1. Dietary recommendations for CKD stage G1 to G5

Stage (GFR)	Energy (kcal/kgBW/day)	Protein (g/kgBW/day)	Salt (g/day)	Potassium (mg/day)
Stage 1 (GFR ≥90)	25 to 35	Avoid excessive intake	3≤ <6	No restraint
Stage 2 (GFR 60 to 89)		Avoid excessive intake		No restraint
Stage 3a (GFR 45 to 59)		0.8 to 1.0		No restraint
Stage 3b (GFR 30 to 44)		0.6 to 0.8		≤2 000
Stage 4 (GFR 15 to 29)		0.6 to 0.8		≤1 500
Stage 5 (GFR <15)		0.6 to 0.8		≤1 500
5D (on dialytic therapy)	Attached table			

Note) The intake of energy and nutrients is adjusted to be the appropriate volume depending on the disease condition, in accordance with guidelines for complicating diseases (diabetes mellitus, obesity, etc.), etc. It varies depending on gender, age, physical activity.
Note) For body weight, the standard weight (BMI = 22) is used.

Table 2. Dietary recommendations for CKD stage G5D

Stage 5D	Energy (kcal/kgBW/day)	Protein (g/kgBW/day)	Salt (g/day)	Water	Potassium (mg/day)	Phosphorus (mg/day)
Hemodialysis (3 times a week)	30 to 35[Note 1, 2)]	0.9 to 1.2[Note 1)]	< 6[Note 3)]	As small as possible	≤2 000	≤ protein (g) × 15
Peritoneal dialysis	30 to 35[Note 1, 2, 4)]	0.9 to 1.2[Note 1)]	Volume of water removed at PD (L) × 7.5 + Urine output (L) × 5	Volume of water removed at PD + Urine output	No restraint[Note 5)]	≤ protein (g) × 15

Note 1) For body weight, the standard weight (BMI = 22) is used.
Note 2) Varies depending on gender, age, complicated disease, and physical activity.
Note 3) Adjusted when necessary by taking into account urine output, physical activity, body type, nutrition status, and an increase in body weight during dialysis.
Note 4) The energy from glucose absorbed in peritoneal dialysis is subtracted.
Note 5) When hyperkalaemia is observed, it is restrained in the same way at hemodialysis.

2) Dietary recommendations for Patients on Chronic Dialysis (Journal of the Japanese Society for Dialysis Therapy. 2014; 47: 287-91.)

The following are stated regarding nutrition control for patients on chronic dialysis:

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- What is most important in the diet intake of patients on chronic dialysis is the balance with the dialysis volume. As dialysis programs such as long-hour dialysis have varied in recent years, it will not be sufficient to only propose a uniform diet criterion.
- It is necessary to assess the dialysis volume, diet intake, and the clinical findings and resulting laboratory test figures on a regular basis and to provide feasible instructions according to the life style of each patient in cooperation with people in various job categories in the clinical settings.

3) Clinical Practice Guideline for Acute Kidney Injury 2016 (The Japanese Journal of Nephrology. 2017; 59: 419–533.)

The following are provided regarding nutrition control of patients with acute kidney injury (hereinafter referred to as "AKI") (The recommendation level; 2[9], evidence level; D[10]).

- For the dose of energy and protein, nutrition therapy will be proposed based on the severity of AKI and underlying disease.
- When applicable, nutrition therapy is provided gastrointestinally to patients with severe AKI, and intake of protein will not be severely restricted unless accompanied by severe electrolyte abnormality.

The following are provided as well regarding nutrition control for patients on renal replacement therapy including dialysis or hemofiltration.

- Administration of protein at 0.8 to 1.0 g/kg/day is recommended for patients with AKI who do not need renal replacement therapy and who are not under hypercatabolism. In particular, during continuous renal replacement therapy (hereinafter referred to as "CRRT"), approximately 10 to 15 g/day of amino acid may be lost. If the intake of protein is less than 1 g/kg/day, the nitrogen-depleted condition may be worsened as a result in patients on renal replacement therapy. Therefore, the guideline of the Kidney Disease Improving Global Outcomes (KDIGO) recommends the intake of 1.7/kg/day of protein to account for the amount for protein loss in patients under hypercatabolism on CRRT. It also reports that a protein intake of 2.5 g/kg/day is needed to achieve a positive nitrogen balance in patients on CRRT. However, it has been pointed out that excessive intake of amino acid can result in azotaemia, extending the duration of renal replacement therapy.
- Patients on CRRT may experience hypokalaemia and hypophosphataemia due to commercially available dialysate/refilled solution. There is a report that hypophosphataemia delays withdrawal from a ventilator. Proper replenishment by parenteral or enteral nutrition may be useful in some cases. Meanwhile, electrolyte abnormality often occurs when CRRT is shifted to intermittent renal replacement therapy. It is necessary to review the details of parenteral or enteral nutrition including total volume of infusion solution. Special attention should be paid to hyperkalaemia.

4) Guideline for parenteral and enteral nutrition Version 3 (Japanese Society for

[9]Recommendation level; 2: Strongly recommended (proposed).
[10]Evidence level; D: Very weak: Hardly sure

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Parenteral and Enteral Nutrition, 2013)

The section on renal failure provides the following regarding recommended parenteral nutrition preparations for patients on dialysis or hemofiltration.

- The appropriate composition of nutrition should be considered for each patient with acute renal failure (hereinafter referred to as "ARF") (AIII[11])
  - Handling of administration for parenteral nutrition in patients with ARF is the same as that for enteral nutrition.
  - For patients with ARF, it is recommended to use parenteral nutrition preparations with the standard composition, in principle. At the same time, extreme caution should be exercised to electrolyte abnormality.
- When enteral nutrition is administered to patients on hemodialysis and on continuous ambulatory peritoneal dialysis (hereinafter referred to as "CAPD"), enteral nutrition preparations with the standard composition should be used. (AIII)
  - As renal function has been compensated in patients on hemodialysis or patients who started CAPD, not only lack of protein but also hypokalaemia and/or hypophosphataemia will occur after these patients receive enteral nutrition preparations with protein/electrolyte restricted. Therefore, it is more beneficial to use enteral nutrition preparations[12] of the standard composition.
- Patients with chronic renal failure (hereinafter referred to as "CRF") should receive amino acid preparations for renal failure. (BIII[13])
  - For administration of amino acid preparations for renal failure to patients with CRF, there is limited evidence for its usefulness. However, they are rational preparations and are recommended for use.

Of note, for amino acid preparations for renal failure, a separate section provides a statement that they are designed to avoid nitrogen load before introduction of hemodialysis and to prevent malfunction of the urea cycle.

5) ESPEN Guidelines on Parenteral Nutrition: Adult Renal Failure (ESPEN, 2009)

Guidelines on nutrition control in Europe provide the following regarding the recommended parenteral nutrition preparations for patients on dialysis or hemofiltration:

- Standard formulae are adequate for the majority of patients with ARF. However, requirements can differ from patient to patient and have to be assessed individually. When there are electrolyte derangements, formulae without electrolytes or customized formulae can be advantageous (Grade C[14]).
- In acutely ill patients with CKD on hemodialysis, the decision to use parenteral nutrition should be based on the same criteria as in ARF patients (Grade C).

[11] AIII; Recommended ranking A: Strongly recommended
Clinical-research-paper ranking III: Case accumulation study and expertise opinions
[12] Preparations that are not condition-specific ones.
[13] BIII; Recommended ranking B: Generally recommended
Clinical-research-paper ranking III: Case accumulation study and expertise opinions
[14] Grade C: Experts' opinions or clinical experience

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- Acutely ill CAPD patients with CKD have the same parenteral nutrition requirements as ARF patients (Grade C).

6) A.S.P.E.N. Clinical Guidelines: Nutrition Support in Adult Acute and Chronic Renal Failure (American Society for Parenteral and Enteral Nutrition, 2010)

For parenteral nutrition preparations recommended for patients on dialysis or hemofiltration, US guidelines on nutrition control provide a statement that standard amino acid parenteral nutrition formulations should be used in acute kidney injury. (Grade C[15]). No specific parenteral nutrition preparations are mentioned to be used in patients on dialysis or hemofiltration.

7) Evidence-based Clinical Practice Guidelines for Liver Cirrhosis 2015 (2nd Edition) (The Japanese Society of Gastroenterology, 2015)

For branched-chain amino acid (BCAA) that is contained abundantly in amino acid preparations for hepatic failure, the Evidence-based Clinical Practice Guidelines for Liver Cirrhosis (2nd Edition) provide a statement that administration of BCAA infusion preparations is recommended to patients with disturbed consciousness of hepatic encephalopathy including coma (Recommendation level; 1[16], Evidence level; A[17]). The guidelines do not mention administration to patients on dialysis or hemofiltration.

8) Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (American Association for the Study of Liver Diseases/The European Association for the Study of the Liver, 2014)

The guidelines for hepatic encephalopathy in the US and Europe in patients with chronic liver disorder provide the following regarding BCAA, which are contained abundantly in amino acid preparations for hepatic failure.

- An updated meta-analysis of 8 randomized, controlled trials (RCTs) indicated that oral BCAA-enriched formulations improve the manifestations of episodic hepatic encephalopathy whether it is overt or latent. There is no effect of IV BCAA parenteral formulations on the episodic hepatic encephalopathy.

The guidelines do not mention administration to patients on dialysis or hemofiltration.

3. The relevant statements in overseas package inserts

No parenteral nutrition preparations or amino acid preparations for hepatic failure commercially available in Japan are identical to those marketed in the US and Europe. The following are the statements in the relevant package inserts in the UK, Germany, France, and the US which have been submitted by the marketing authorization holders:

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[15] Grade C: Supported by at least one level II investigation
Level II: Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error

[16] Recommendation level; 1: Strongly recommended. Implementation is recommended.

[17] Evidence level; A: High-quality evidence (high) The real effect is surely approximate to the estimate of the effect.

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(1) Statements in the package inserts in the UK

The following are the results obtained regarding drugs commercially available in the UK that have been identified in the British National Formulary (BNF78 September 2019-march2020) and checked for the statements in the package inserts.

1) Amino acid preparations

The package insert of some amino acid preparations (not including amino acid preparations for hepatic failure) specifies “patients with serious renal failure who are not on renal replacement therapy” in the Contraindications section. The package inserts of other products do not specify patients on dialysis or hemofiltration in the Contraindications section.

Since no relevant documents mentioned amino acid preparations for hepatic failure, it was not possible to check the statements in the Contraindications section for the preparations.

2) PPN preparations/TPN preparations

The package inserts of some PPN preparations and TPN preparations specified “patients with serious renal disorder who are not on renal replacement therapy” in the Contraindications section. In the package inserts of other products, patients on dialysis or hemofiltration were also not specified in the Contraindications section.

(2) Statements in the package inserts in Germany

The following are the results obtained regarding drugs commercially available in Germany that have been identified in the German drug lists (ROTE LISTE 2019) and checked for the statements in the package inserts.

1) Amino acid preparations

The package insert of some amino acid preparations (not including amino acid preparations for hepatic failure) specified “patients with serious renal failure” in the Contraindications section. The package inserts of other products did not specify patients on dialysis or hemofiltration in the Contraindications section.

For amino acid preparations for hepatic failure, “patients with renal failure” were specified in the Contraindications section in some products. Other products were not contraindicated in patients on dialysis or hemofiltration.

2) PPN preparations/TPN preparations

The package inserts of some PPN preparations and TPN preparations specified “patients with serious renal disorder who are not on renal replacement therapy” in the Contraindications section. The package inserts of other products did not specify patients on dialysis or hemofiltration in the Contraindications section.

(3) Statements in the package inserts in France

The following are the results obtained regarding drugs commercially available in France that have been identified in the French drug lists (VIDAL 2019) and checked for the statements in the

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package inserts.

1) Amino acid preparations/PPN preparations/TPN preparations

"Patients with serious renal failure who are not on renal replacement therapy" were specified in the Contraindications section. Since the book did not mention amino acid preparations for hepatic failure, it was not possible to check the statements in the Contraindications section for the preparations.

(4) Statements in the package inserts in the US

The following are the results obtained regarding drugs commercially available in the US that have been identified in the US drug lists (Drug facts and comparisons 2017) and checked for the statements in the package inserts.

1) Amino acid preparations

For some amino acid preparations (not including amino acid preparations for hepatic failure), "patients with untreated anuria," "patients with anuria," or "patients with serious renal disorder" were specified in the Contraindications section. The package inserts of other products did not specify patients on dialysis or hemofiltration in the Contraindications section.

In addition, for amino acid preparations for hepatic failure, "patients with anuria" was specified in the Contraindications section.

2) PPN preparations/TPN preparations

Patients on dialysis or hemofiltration were not specified in the Contraindications section.

4. Studies and reports on measures taken

There were no studies or reports on measures taken related to the use of drugs investigated for patients on dialysis or hemofiltration submitted by the marketing authorization holders to PMDA by March 5, 2020.

5. Adverse reaction case reports

The marketing authorization holders reported to PMDA by March 5, 2020 the following adverse reactions in Japanese patients [18] on dialysis or hemofiltration who received the drugs investigated: 4 cases ("injection site ulcer," "cellulitis," "injection site phlebitis," and "pyrexia") in 2 patients on Bfluid Injection (branded name); and 3 cases ("hypoglycaemia," "hepatic encephalopathy" and "increased ammonia") in 3 patients on Aminoleban Injection (branded name). Outcomes were all 'recovered' except 'not recovered' for the case of "injection site ulcer"

[18] Of the 13 patients for whom "dialysis" or "hemofiltration" was stated in the clinical course section, physician's comment, reporting company's comment, history of primary illness/complication/past illness in the case report form, 8 patients were excluded because they did not use any of the drugs investigated for patients on dialysis or hemofiltration. That is, the following patients were excluded: 1 patient who received an investigation item after withdrawal of continuous hemofiltration dialysis, 1 patient who was described as "dialysis was refused," and 6 patients who underwent dialysis or hemofiltration for treatment of adverse events.

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and 'unknown' for the case of "increased ammonia" (Appendix 2). Of note, the clinical course section for the patient whose outcome of "increased ammonia" was 'unknown' stated that "the ammonia level was decreased after treatment with the drug was discontinued, and plasma exchange therapy was performed."

There were no overseas adverse-reaction reports on patients on dialysis or hemofiltration who received drugs investigated from the marketing authorization holders submitted to PMDA by March 5, 2020.

IV. PMDA's judgment based on investigation results

1. Exclusion of patients on dialysis or hemofiltration from "patients with serious renal disorder" in the Contraindication section

Patients with chronic renal disorder and acute kidney injury should take more protein after introduction of dialysis than before its introduction, and appropriate nutrition control customized for individual patients is required. ("III 2.1) Dietary recommendations for chronic kidney disease, 2014," "III 2.2) Dietary recommendations for Patients on Chronic Dialysis," and "III 2.3) Clinical Practice Guideline for Acute Kidney Injury (AKI)"). The necessity of amino acid preparations with the standard composition can be understood because administration of the required amount of protein with an amino acid agent for renal failure currently marketed in Japan will result in a heavier moisture load.

The guidelines for nutrition control in Japan and overseas recommend that patients on dialysis receive parenteral nutrition preparations or amino acid preparations with the standard composition. ("III 2.4) Guideline for parenteral and enteral nutrition Version 3" and "III 2.5) ESPEN Guidelines on Parenteral Nutrition: Adult Renal Failure").

Meanwhile, even though excessive water/electrolyte, accumulated urea, etc. due to parenteral nutrition preparations are quoted as the rationale for contraindication, they are considered to be properly controlled overseas because the preparations are not contraindicated overseas in patients on dialysis or hemofiltration. They would be also properly controlled in Japan based on the following reasons:

- A certain volume of urea can be removed by dialysis, hemofiltration ("III 1. Volume of water, electrolyte, and urea removed by dialysis or hemofiltration")
- Although the "Blood purifier (hollow fiber type) function category 2013" does not mention the volume of water and electrolyte removed, the removal of excessive water and electrolyte is a purpose of dialysis or hemofiltration.

Of note, although guidelines mentioned less about nutrition control for patients on hemofiltration than that for patients on dialysis, the same level of nutrition control as that for patients on dialysis is required for those on hemodialysis, too. Excessive volume of water, electrolyte, urea, etc. due to parenteral nutrition preparations should be properly controlled in patients on hemodialysis at the same level for those on dialysis.

As with parenteral nutrition preparations, when amino acid preparations for hepatic failure are administered to patients on dialysis or hemofiltration, the drug-induced, accumulated urea, etc. is removed to some extent by dialysis or hemofiltration and excessive urea should be properly

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controlled, too.

Of note, as for BCAA that is contained abundantly in amino acid preparations for hepatic failure, some overseas guidelines state that parenteral preparations that contain a higher percentage of BCAA (hereinafter referred to as "BCAA preparations") have not shown any effectiveness in transient hepatic encephalopathy, presenting related reports in 1989 as references. The Japanese guidelines, on the other hand, mentioned the difficulties in evaluating the effectiveness of BCAA preparations in patients with hepatic cirrhosis. Although the effectiveness has been supported by RCTs and guidelines, some systematic reviews suggested the lack of definite effectiveness in that respect, and there are meta-analyses with seemingly conflicting results. Moreover, several comparative studies of BCAA preparations were conducted in the 1980s and are not fit for today's discussion on bias risks. The guidelines further stated that some high-quality randomized studies in recent years have reported BCAA preparations improve the parameter of hepatic encephalopathy and finally strongly recommended BCAA preparations for treatment of disturbed consciousness of hepatic encephalopathy including coma. ("III 2.7) Evidence-based Clinical Practice Guidelines for Liver Cirrhosis (2nd Edition)" and "III 2.8) Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver"). Therefore, it is considered that administration of amino acid preparations for hepatic failure is nonetheless recommended to patients with hepatic encephalopathy.

PMDA considers that it is acceptable to exclude patients on dialysis or hemofiltration from "patients with serious renal disorder" in the Contraindication section. However, the volumes of electrolyte, urea nitrogen, body fluid, etc. are expected to fluctuate by dialysis or hemofiltration, or administration of parenteral nutrition preparations or amino acid preparations for hepatic failure. Therefore, precautions should be issued that results of blood chemistry, body-fluid balance, etc. should be assessed before and during administration of parenteral nutrition preparations or amino acid preparations for hepatic failure, to determine whether to start and continue administration with the patient's conditions monitored.

2. Exclusion of patients on dialysis or hemofiltration from "patients with azotaemia" and "patients with oliguria" in the Contraindication section

The package inserts of amino acid preparations, PPN preparations, and TPN preparations specify "patients with azotaemia" in the Contraindications section. In addition, PPN preparations and TPN preparations are contraindicated in "patients with oliguria." "Patients with azotaemia" and "patients with oliguria" include "patients with serious renal disorder" in terms of the conditions. In the patients on dialysis or hemofiltration of those patients, it is considered that excessive volumes of water, electrolyte, urea, etc. caused by parenteral nutrition preparations would be properly controlled, as mentioned above. Therefore, in association with the exclusion of patients on dialysis or hemofiltration from "patients with serious renal disorder" specified in the Contraindications, it is considered to be acceptable to exclude patients on dialysis or hemofiltration from "patients with azotaemia" and "patients with oliguria," who are specified in the Contraindications.

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3. Revision in Contraindications and Precautions in the package inserts

Based on IV. 1 and 2, PMDA determined it appropriate to revise Contraindications and Precautions as follows:

Amino acid preparations

- To exclude patients on dialysis or hemofiltration from “patients with serious renal disorder” and “patients with azotaemia” in the Contraindications section.
- Of the patients with serious renal disorder or patients with azotaemia that have been excluded from the Contraindication, those on dialysis or hemofiltration should be added in the Careful Administration.
- Regarding those on dialysis or hemofiltration of patients with serious renal disorder or patients with azotaemia who have been excluded from the Contraindications, a statement should be added that the volume of urea removed and accumulated varies depending on the dialysis method and patients’ conditions and initiation and continuation of administration should be determined after the patient’s condition is carefully checked based on assessment of blood biochemistry, body-fluid balance, etc.

PPN preparations and TPN preparations

- To exclude patients on dialysis or hemofiltration from “patients with serious renal disorder,” “patients with azotaemia,” and “patients with oliguria” in the Contraindications section.
- Of the patients with serious renal disorder, patients with azotaemia, or patients with oliguria, who have been excluded in the Contraindication, those on dialysis or hemofiltration should be added in the Careful Administration.
- Regarding those on dialysis or hemofiltration of patients with serious renal disorder or patients with azotaemia or oliguria who have been excluded from the Contraindications, a statement should be added that the volume of water, electrolytes, or urea removed and accumulated varies depending on the dialysis method and patients’ conditions and initiation and continuation of administration should be determined after the patient’s condition is carefully checked based on assessment of blood biochemistry, body-fluid balance, etc.

Amino acid preparations for hepatic failure

- To exclude patients on dialysis or hemofiltration should be excluded from “patients with serious renal disorder” in the Contraindication section.
- Of the patients with serious renal disorder who have been excluded in the Contraindication, those on dialysis or hemofiltration should be added in the Careful Administration.
- Regarding those on dialysis or hemofiltration of patients with serious renal disorder who have been excluded from the Contraindications, a statement should be added that the volume of urea removed and accumulated varies depending on the dialysis method and patients’ conditions and initiation and continuation of administration should be determined after the patient’s condition is carefully checked based on assessment of blood biochemistry, body-

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fluid balance, etc.

It was also decided that the present inconsistencies between preparations in description in relevant sections of package inserts needed to be addressed in association with the revision.

V. Expert discussions

The PMDA's judgment was supported by the experts. The following comment was raised from some of the experts:

Since amino acid preparations for hepatic failure contain acidic amino acid abundantly, acidosis is still of concern in patients with renal failure (including those with anuria) on dialysis. A precaution should be issued with acid-base equilibrium included in the requirement for assessment.

Based on the expert opinion and considering that administration of amino acid preparations (including those for hepatic failure) may affect the acid-base equilibrium, that administration mixed with amino acid is assumed for TPN basic solution as well, as indicated in the Dosage and Administration section of the package insert, PMDA decided that a precaution should be issued with acid-base equilibrium included in the requirement for assessment for all the drugs investigated this time.

VI. Overall assessment

Following the above discussion, PMDA concluded that excluding "patients on dialysis or hemofiltration" from the "patients with serious renal disorder," "patients with azotaemia," and "patients with anuria" was acceptable and revision of the package insert reflecting the following as presented in the Appendix 3 (The Appendix 3 is not included. See the Detailed information on revisions of PRECAUTIONS.) was necessary.

・ The "Patients on dialysis or hemofiltration" that have been excluded from the Contraindications section should be subjected to "Careful Administration."

・A statement should be added in the Important Precautions section that the volume of urea removed and accumulated varies depending on the dialysis method and patients' conditions and initiation and continuation of administration should be determined after the patient's condition is carefully checked based on assessment of blood chemistry, acid-base equilibrium, body-fluid balance, etc.

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Appendix 1

	Brand name	Authorization holder	Indications	Dosage and administration
Amino acid agents	(1) Amizet B Infusion Solution	Terumo Corporation	Amino acid supplementation under the following condition: Hypoproteinaemia, undernutrition state, before/after surgery	< Administration in peripheral veins > The usual adult dose is 200 to 400 mL administered slowly as intravenous drip infusion. The dosing speed is desired to be 60 minutes for approximately 10 g of amino acid when administered in the body. The usual standard speed for adults is 120 minutes per 200 mL. The injection should be slower in pediatric and elderly patients, and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. It should be with a glucose injection agent for effective use of biological amino acid. < Administration in central veins > The usual adult dose of 400 to 800 mL/day is administered in the central vein by the high-calorie injection method as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight.
	(2) Aminic Infusion Solution	AY Pharmaceuticals Co., Ltd.	Amino acid supplementation under the following condition: Hypoproteinaemia, undernutrition state, before/after surgery	At administration in peripheral veins The usual adult dose is 200 to 400 mL administered gradually as intravenous drip infusion. The dosing speed is desired to be 60 minutes for approximately 10 g of amino acid when administered in the body. The usual standard speed for adults is 120 minutes per 200 mL. The injection should be slower in pediatric and elderly patients, and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. It should be simultaneously administered with a glucose injection agent for effective use of biological amino acid. At administration in central veins The usual adult dose of 400 to 800 mL/day is administered in the central vein by the high-calorie injection method as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight.

	(3) Amiparen Injection	Otsuka Pharmaceutical Factory, Inc.	Amino acid supplementation under the following condition: Hypoproteinaemia, undernutrition state, before/after surgery	Administration in central veins The usual adult dose of 400 to 800 mL/day is administered in the central vein by the high-calorie injection method as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. Administration in peripheral veins The usual adult dose is 200 to 400 mL administered gradually as intravenous drip infusion. The dosing speed is desired to be 60 minutes for approximately 10 g of amino acid when administered in the body. The usual standard speed for adults is 60 minutes per 100 mL. The injection should be slower in pediatric and elderly patients, and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. It should be simultaneously administered with a glucose injection agent for effective use of biological amino acid.
	(4) Hy-Pleamin Injection	Fuso Pharmaceutical Industries, Ltd.	Amino acid supplementation under the following condition: Hypoproteinaemia, undernutrition state, before/after surgery	The usual adult dose is 20 to 500 mL administered gradually as intravenous injection or intravenous drip infusion. The dosing speed is desired to be 60 minutes for approximately 10 g of amino acid when administered in the body. The usual standard speed for adults is 80 to 100 minutes per 200 mL. The injection should be slower in pediatric and elderly patients, and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. It should be simultaneously administered with a glucose injection agent for effective use of biological amino acid.
	(5) Hy-Pleamin S Injection	Fuso Pharmaceutical Industries, Ltd.	Amino acid supplementation under the following condition: Hypoproteinaemia, undernutrition state, before/after surgery	The usual adult dose is 20 to 500 mL administered gradually as intravenous injection or intravenous drip infusion. The dosing speed is desired to be 60 minutes for approximately 10 g of amino acid when administered in the body. The usual standard speed for adults is 80 to 100 minutes per 200 mL. The injection should be slower in pediatric and elderly patients, and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. Of note, the maximum daily dose is 100 g of D-sorbitol.

	(6) Plas-Amino Injection	Otsuka Pharmaceutical Factory, Inc.	Amino acid supplementation under the following condition: Hypoproteinaemia, undernutrition state, before/after surgery	The usual adult dose is 500 to 1 000 mL administered as intravenous drip infusion. The dosing speed is desired to be 60 minutes for approximately 10 g of amino acid when administered in the body. The usual standard speed for adults is 90 to 120 minutes per 500 mL. The injection should be slower in pediatric and elderly patients, and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight.
	(7) Pleamin-P Injection	Fuso Pharmaceutical Industries, Ltd.	It is used for amino acid supplementation to neonates, babies, and infants aged 1 to 3 years under the following conditions: Note that neonates are defined to have body weight of 2 kg or more at birth, in principle. Hypoproteinaemia, undernutrition state, before/after surgery	The usual dose of amino acid is administered at 1.75 to 2.75 g (23 to 36 mL of this product)/kg body weight/day, or 1.50 to 2.50 g (20 to 33 mL of this product)/kg body weight/day for neonates (with the body weight of 2 kg or more at birth) and infants aged 1 to 3 years old in the central vein by the high-calorie injection method as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the clinical symptoms and laboratory results
	(8) Proteamin 12 Injection	Terumo Corporation	Amino acid supplementation under the following condition: ・When the patient experiences any disturbances in intake or absorption of protein, such as condition before/after surgery, gastrointestinal disturbance, and diet restriction. ・Substantial loss of protein due to surgery, thermal burn, etc. ・Poor oral intake in addition to hypoproteinaemia due to various diseases	The usual adult dose is 200 mL of this product administered as intravenous drip infusion. The standard infusion speed of this product is 120 minutes per 200 mL. When using the central-vein nutrition method, mix carbohydrate solution, etc. with this product and inject it in the central vein continuously over 24 hours. Note that the dose should be adjusted when necessary, depending on the age and symptom.

			・Substantial increase in demand as well as consumption, such as febrile/wasting diseases	
	(9) Moriamin-S Injection	AY Pharmaceuticals Co., Ltd.	Amino acid supplementation under the following condition: Hypoproteinaemia, undernutrition state, before/after surgery	The usual adult dose is 20 to 500 mL administered gradually as intravenous injection or intravenous drip infusion. The dosing speed is desired to be 60 minutes for approximately 10 g of amino acid when administered in the body. The usual standard speed for adults is 80 to 100 minutes per 200 mL. The injection should be slower in pediatric and elderly patients, and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. It should be simultaneously administered with a glucose injection agent for effective use of biological amino acid.
	(10) Moripron-F Infusion Solution	AY Pharmaceuticals Co., Ltd.	Amino acid supplementation under the following condition: Hypoproteinaemia, undernutrition state, before/after surgery	At administration in peripheral veins The usual adult dose is 200 to 400 mL administered gradually as intravenous drip infusion. The dosing speed is desired to be 60 minutes for approximately 10 g of amino acid when administered in the body. The usual standard speed for adults is approximately 120 minutes per 200 mL. The injection should be slower in pediatric and elderly patients, and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. It should be simultaneously administered with a glucose injection agent for effective use of biological amino acid. At administration in central veins The usual adult dose of 400 to 800 mL/day is administered in the central vein by the high-calorie injection method as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight.

	Brand name	Authorization holder	Indications	Dosage and administration
Nutrition agents for peripheral veins	(11) Amicaliq Infusion Solution	Terumo Corporation	Supplementation of amino acid, electrolyte, and water under the following conditions: ・Poor oral intake, and under a condition of mild hypoproteinaemia or mild undernutrition ・Before/after surgery	The usual adult dose is 500 mL administered in the peripheral vein as intravenous drip infusion. The usual dosing speed for adults is 120 minutes per 500 mL. The injection should be slower in elderly patients and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. The maximum daily dose is 2500 mL/day.
	(12) Twinpal Infusion Solution	AY Pharmaceuticals Co., Ltd.	Supplementation of amino acid, electrolyte, and water under the following conditions: ・Poor oral intake, and under a condition of mild hypoproteinaemia or mild undernutrition ・Before/after surgery	Before preparation, break the center seal between two layers and mix the I-layer solution and the II-layer solution well. The usual adult dose is 500 mL administered in the peripheral vein as intravenous drip infusion. The usual dosing speed for adults is 120 minutes per 500 mL. The injection should be slower in elderly patients and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. The maximum daily dose is 2500 mL/day.
	(13) Paresafe Infusion Solution	AY Pharmaceuticals Co., Ltd.	Supplementation of amino acid, electrolyte, vitamin B_1 and water under the following conditions: ・Poor oral intake, and under a condition of mild hypoproteinaemia or mild undernutrition ・Before/after surgery	Before preparation, break the center seal between the two chambers and mix the two solutions well in the large chamber and in the small chamber. The usual adult dose is 500 mL administered in the peripheral vein as intravenous drip infusion. The usual dosing speed for adults is 120 minutes per 500 mL. The injection should be slower in elderly patients and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. The maximum daily dose is 2500 mL/day.
	(14) Pareplus Infusion Solution	AY Pharmaceuticals Co., Ltd.	Supplementation of amino acid, electrolyte, water soluble vitamin, and water	Before preparation, break the center seal between the two chambers and mix two solutions in the large chamber and in the small chamber. The usual adult dose is 500 mL administered in the peripheral vein as intravenous drip infusion.

			under the following conditions: ・Poor oral intake, and under a condition of mild hypoproteinaemia or mild undernutrition ・Before/after surgery	The usual dosing speed is 120 minutes per 500 mL. The injection should be slower in elderly patients and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. The maximum daily dose is 2500 mL/day.
	(15) Bfluid Injection	Otsuka Pharmaceutical Factory, Inc.	Supplementation of amino acid, electrolyte, vitamin B_1 and water under the following conditions: ・Poor oral intake, and under a condition of mild hypoproteinaemia or mild undernutrition ・Before/after surgery	Before preparation, break the center seal between the two chambers and mix two solutions in the upper chamber and in the lower chamber. The usual adult dose is 500 mL administered in the peripheral vein as intravenous drip infusion. The usual dosing speed for adults is 120 minutes per 500 mL. The injection should be slower in elderly patients and patients in a serious condition. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. The maximum daily dose is 2500 mL/day.

	Brand name	Authorization holder	Indications	Dosage and administration
The basic solution for central-vein nutrition	(16) Hicaliq NC-L (17) Hicaliq NC-N (18) Hicaliq NC-H Infusion Solution	Terumo Corporation	Water, electrolyte, and caloric supplementation when supplementation by oral or enteral nutrition is impossible or insufficient and central-vein nutrition is the only option.	Hicaliq NC-L/Calonary L This product is used as the initial solution for patients whose glucose tolerance is unknown or decreased at the start of central-vein nutrition therapy or as the maintenance solution for patients who need to restrict glucose intake due to decreased glucose tolerance after an invasive procedure, etc. The initial solution or maintenance solution should be the one without sodium or chloride contained in this product 700 mL or the one mixed well with 10 to 12% amino-acid injection solution 200 to 300 mL with less sodium and chloride contained. The usual daily dose for adults is 1 800 to 2 000 mL of the initial solution or maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. Hicaliq NC-N and Hicaliq NC-H Calonary M and Calonary H This product is used as the maintenance solution for central-vein nutrition therapy. The maintenance solution should be the one without sodium or chloride contained in this product 700 mL or the one mixed well with 10 to 12% amino-acid injection solution 300 to 400 mL with less sodium and chloride contained. The usual daily dose for adults is 2 000 to 2 200 mL for the maintenance administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight.
	(19) Calonary L (20) Calonary M (21) Calonary H Infusion Solution (Generics each for Hicaliq NC-L, Hicaliq NC-N, Hicaliq NC-H Infusion Solution)	Fuso Pharmaceutical Industries, Ltd.		
	(22) Hicaliq-1 (23) Hicaliq-2 (24) Hicaliq-3 Liquid	Terumo Corporation	They are used for nutritional supplementation by central-vein nutrition therapy when enteral nutrition is	Hicaliq-1 The initial solution for central-vein nutrition therapy is created by mixing this product 700 mL with 200 to 300 mL of amino acid injection at 10% or 12 %. The usual daily dose for adults is 1800 to 2000 mL of the initial solution administered in the central vein over

			impossible or insufficient, or suspended.	24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, body weight, and symptom. Hicaliq-2 and Hicaliq-3 The maintenance solution for central-vein nutrition therapy is created by mixing this product 700 mL well with 300 to 400 mL of amino acid injection at 10% or 12 %. The usual daily dose for adults is 2 000 to 2 200 mL of the maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, body weight, and symptom.
	(25) Rehabix-K1 (26) Rehabix-K2 Infusion Solution	AY Pharmaceuticals Co., Ltd.	They are used for water, electrolyte, and caloric supplementation when supplementation by oral or enteral nutrition is impossible or insufficient and central-vein nutrition is the only option.	Rehabix-K1 This is used as the initial solution for patients whose glucose tolerance is unknown or decreased at the start of central-vein nutrition therapy or as the maintenance solution for patients who need to restrict glucose intake due to decreased glucose tolerance after an invasive procedure, etc. The initial or maintenance solution for pediatrics is created by mixing this product 500 mL well with 50 to 100 mL of amino acid injection at 10% or 12%. The usual daily dose for pediatrics is the following volumes of the initial solution or maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Daily dose per 1 kg of body weight (mL/kgBW/day) Less than 1 year old: 80 to 150 1 to 5 years old: 80 to 130 6 to 10 years old: 60 to 100 11 to 15 years old: 35 to 60 Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight. Rehabix-K2 This product is used as the maintenance solution for central-vein nutrition therapy. The maintenance solution for pediatrics is created by mixing this product 500 mL well with 100 to 200 mL of amino acid injection at 10% or 12 %. The usual daily dose for pediatrics is the following volumes of the maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Daily dose per 1 kg of body weight (mL/kgBW/day) Less than 1 year old: 80 to 150

				1 to 5 years old: 80 to 130 6 to 10 years old: 60 to 100 11 to 15 years old: 35 to 60 Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight.

	Brand name	Authorization holder	Indications	Dosage and administration
Kit agents for central-vein nutrition	(27) Elneopa-NF No.1 (28) Elneopa-NF No.2 Injection	Otsuka Pharmaceutical Factory, Inc.	Supplementation of water, electrolyte, calorie, amino acid, vitamins, zinc, iron, copper, manganese, and iodine when supplementation by oral or enteral nutrition is impossible or insufficient and central-vein nutrition is the only option	Elneopa-NF No.1 Injection This product is used as the initial solution for patients whose glucose tolerance is unknown or decreased at the start of central-vein nutrition therapy or as the maintenance solution for patients who need to restrict glucose intake due to decreased glucose tolerance after an invasive procedure, etc. Before preparation, break the center seal between the 2 upper and lower chambers and open the small yellowish brown and reddish brown chambers in the upper chamber simultaneously to mix them well and use the drug as the initial or maintenance solution. The usual daily dose for adults is 2 000 mL of the initial solution or maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight. Elneopa-NF No.2 Injection This product is used as the maintenance solution for central-vein nutrition therapy. Before preparation, break the center seal between the 2 upper and lower chambers and open the small yellowish brown and reddish brown chambers in the upper chamber simultaneously to mix them well and use the drug as the maintenance solution. The usual daily dose for adults is 2 000 mL of the maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight.
	(29) Neoparen No.1 (30) Neoparen No.2 Injection	Otsuka Pharmaceutical Factory, Inc.	Supplementation of water, electrolyte, calorie, amino acid, and vitamins when supplementation by oral or enteral nutrition is impossible or insufficient	Neoparen No.1 Injection This product is used as the initial solution for patients whose glucose tolerance is unknown or decreased at the start of central-vein nutrition therapy or as the maintenance solution for patients who need to restrict glucose intake due to decreased glucose tolerance after an invasive procedure, etc. Before preparation, break the center seal between the 2 upper and

			and central-vein nutrition is the only option	lower chambers and open the small yellowish brow chamber in the upper chamber simultaneously to mix them well and use the drug as the initial or maintenance solution. The usual daily dose for adults is 2 000 mL of the initial solution or maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight. Neoparen No.2 Injection This product is used as the maintenance solution for central-vein nutrition therapy. Before preparation, break the center seal between the 2 upper and lower chambers and open the small yellowish brown chamber in the upper chamber simultaneously to mix them well and use the drug as the maintenance solution. The usual daily dose for adults is 2 000 mL of the maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight.
	(31) Pntwin No.1 (32) Pntwin No.2 (33) Pntwin No.3 Infusion Solution	AY Pharmaceuticals Co., Ltd.	Supplementation of water, electrolyte, amino acid, and calorie when supplementation by oral or enteral nutrition is impossible or insufficient and central-vein nutrition is the only option	Pntwin No.1 This is used as the initial solution for patients whose glucose tolerance is unknown or decreased at the start of central-vein nutrition therapy or as the maintenance solution for patients who need to restrict glucose intake due to decreased glucose tolerance after an invasive procedure, etc. Before preparation, break the center seal between two layers and mix the I-layer solution and the II-layer solution to use it as the maintenance or initial solution. The usual daily dose for adults is 2 000 mL of the initial solution or maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight. Pntwin No.2 This product is used as the maintenance solution for central-vein nutrition therapy. Before preparation, break the center seal between two layers and

				mix the I-layer solution and the II-layer solution to use it as the maintenance. The usual daily dose for adults is 2 200 mL of the maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight. Pntwin No.3 This product is used as the maintenance solution for central-vein nutrition therapy. Before preparation, break the center seal between two layers and mix the I-layer solution and the II-layer solution to use it as the maintenance. The usual daily dose for adults is 2 400 mL of the maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight.
	(34) Fulcaliq 1 (35) Fulcaliq 2 (36) Fulcaliq 3 Infusion Solution	Terumo Corporation	Supplementation of water, electrolyte, calorie, amino acid, and vitamins when supplementation by oral or enteral nutrition is impossible or insufficient and central-vein nutrition is the only option	Fulcaliq 1 This product is used as the initial solution for patients whose glucose tolerance is unknown or decreased at the start of central-vein nutrition therapy or as the maintenance solution for patients who need to restrict glucose intake due to decreased glucose tolerance after an invasive procedure, etc. The usual daily dose for adults is 1 806 mL administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. Fulcaliq 2 This product is used as the maintenance solution for central-vein nutrition therapy. The usual daily dose for adults is 2 006 mL administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. Fulcaliq 3 This product is used as the maintenance solution for central-vein nutrition therapy.

				The usual daily dose for adults is 2 206 mL administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight.
	(37) Mixid L (38) Mixid H Injection	Otsuka Pharmaceutical Factory, Inc.	Supplementation of water, electrolyte, amino acid, fat, and calorie when supplementation by oral or enteral nutrition is impossible or insufficient and central-vein nutrition is the only option	Mixid L Injection This product is used as the initial solution for patients whose glucose tolerance is unknown or decreased at the start of central-vein nutrition therapy or as the maintenance solution for patients who need to restrict glucose intake due to decreased glucose tolerance after an invasive procedure, etc. Before preparation, break the center seal between two chambers and mix the two solutions well in the upper chamber and in the lower chamber to use it as the initial or maintenance solution. The usual daily dose for adults is 1 800 mL of the initial solution or maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight. Mixid H Injection This product is used as the maintenance solution for central-vein nutrition therapy. Before preparation, break the center seal between two chambers and mix the two solutions well in the upper chamber and in the lower chamber to use it as the maintenance solution. The usual daily dose for adults is 1 800 mL of the maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight.
	(39) Onepal No.1 (40) Onepal No.2 Infusion Solution	AY Pharmaceuticals Co., Ltd.	Supplementation of water, electrolyte, amino acid, calorie, vitamins, zinc, iron, copper, manganese, and iodine when supplementation by oral or enteral nutrition is impossible or insufficient	Onepal No.1 This is used as the initial solution for patients whose glucose tolerance is unknown or decreased at the start of central-vein nutrition therapy or as the maintenance solution for patients who need to restrict glucose intake due to decreased glucose tolerance after an invasive procedure, etc. Before preparation, mix the solutions in the large chamber, middle chamber, small T chamber, and small V chamber to use it as the initial or maintenance solution.

			and central-vein nutrition is the only option	The usual daily dose for adults is 1 600 mL of the initial solution or maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight. Onepal No.2 This product is used as the maintenance solution for central-vein nutrition therapy. Before preparation, mix the solutions in the large chamber, middle chamber, small T chamber, and small V chamber to use it as the maintenance solution. The usual daily dose for adults is 1 600 mL of the maintenance solution administered in the central vein over 24 hours as continuous drip infusion. Note that the dose should be adjusted when necessary, depending on the symptom, age, and body weight.

	Brand name	Authorization holder	Indications	Dosage and administration
Amino acid agents for hepatic failure	(41) Aminoleban Injection	Otsuka Pharmaceutical Factory, Inc.	Improvement of encephalopathy when chronic liver disorder occurs	The usual adult dose is 500 to 1 000 mL administered as intravenous drip infusion. The usual dosing speed for adults is 180 to 300 minutes per 500 mL. When using the central-vein nutrition method, mix glucose injection, etc. with this product 500 to 1 000 mL, then inject it in the central vein continuously over 24 hours. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight.
	(42) Terufis Intravenous Drip Infusions (a generic of Aminoleban Injection)	Terumo Corporation		
	(43) Hikarilevan Injection (a generic of Aminoleban Injection)	Hikari Pharmaceutical Co., Ltd.		
	(44) Morihepamin Intravenous Drip Infusions	AY Pharmaceuticals Co., Ltd.	Improvement of encephalopathy when chronic liver disorder occurs	The usual adult dose is 500 mL administered as intravenous drip infusion. The usual dosing speed for adults is 180 minutes or longer per 500 mL. When using the central-vein injection method, mix glucose injection, etc. with this product 500 mL, then inject it in the central vein continuously over 24 hours. Note that the dose should be adjusted when necessary, depending on the age, symptom, and body weight.

Appendix 2

Patients in Japan on dialysis or hemofiltration who received an investigation item and developed adverse reactions

No.	Brand name	Reporting fiscal year	Age	Gender	Primary illness/complication/medical history	Adverse reaction (PT)	Outcome
1	Bfluid Injection	2007	89 years old	Female	Chronic kidney disease, femoral neck fracture, hypothyroidism, diarrhoea, angina pectoris, hypertension	Injection site ulcer	Not recovered
2	Aminoleban Injection	2008	78 years old	Male	Type 2 diabetes mellitus, chronic kidney disease, hepatic cirrhosis, chronic pancreatitis, sepsis	Hypoglycaemia	Recovered
3	Aminoleban Injection	2009	59 years old	Male	Liver disorder, hyperammonaemia, chronic kidney disease	Hepatic encephalopathy	Recovered
4	Aminoleban Injection	2015	67 years old	Male	Hepatic cirrhosis, hemodialysis	Increased ammonia	Unknown
5	Bfluid Injection	2018	83 years old	Female	Chronic renal failure, urinary tract infection, cholecystitis, dementia Alzheimer's type, chronic cardiac failure, catheter infection, dialysis	Cellulitis Injection site phlebitis Pyrexia	Recovered Recovered Recovered