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Summary of Investigation Results

Injectable preparations containing arginine

January 29, 2025

Non-proprietary name

a. to n., p. to u. Not applicable to ethical combination drugs

o. L-lysine hydrochloride/L-arginine hydrochloride

v. L-arginine L-glutamate hydrate

w., x. L-arginine hydrochloride

Brand name (marketing authorization holder)

See attachment.

Japanese market launch

See attachment.

Indications

See attachment.

Summary of revisions

q., s., w., x.

1. “Patients with a history of hypersensitivity to any of the ingredients contained in this drug” should be added to the 9.1 Patients with Complication or History of Diseases, etc. section in 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS.
2. The 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS should be newly added, and “anaphylaxis” should be added.

u.

1. “Patients with a history of hypersensitivity to any of the ingredients contained in this drug (excluding those with a history of hypersensitivity to thiamine chloride hydrochloride)”

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

should be added to the 9.1 Patients with Complication or History of Diseases, etc. section in 9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS.

2. “Anaphylaxis” should be added to “shock” of the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS.

Investigation results and background of the revision

Cases involving anaphylaxis were evaluated. Cases for which a causal relationship of anaphylaxis to several injectable preparations containing arginine (q.*1, s., u., w., x.*1) was reasonably possible have been reported. As a result of consultation with expert advisors regarding the causality assessment of the cases and the necessity of revision of PRECAUTIONS, the MHLW/PMDA concluded that revisions of PRECAUTIONS for these drug preparations were necessary. For certain other drug preparations (b., h., r.), some cases have been reported for which a causal relationship between the drug and the event was reasonably possible. However, the number of reported cases was small and other causes for anaphylaxis, such as concomitant drugs, were also considered to be possible for those cases. Therefore, it was determined that revisions of PRECAUTIONS were not necessary for these drug preparations and those without cases for which a causal relationship between the drug and the event was reasonably possible.

During the course of the review process, in response to the reported cases involving anaphylaxis after administration of the injectable preparations containing only arginine as an active ingredient with no additives, an opinion on the possibility of arginine-induced anaphylaxis as follows was given after seeking views from expert advisors and related academic societies: It is possible that mast cells are directly stimulated by arginine resulting in release of chemical mediators such as histamine (Subramanian H et al. J Allergy Clin Immunol. 2016; 138: 700-10.). Therefore, among injectable preparations containing arginine, drug preparations for which anaphylaxis is not included in the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS were subject to this investigation. However, the necessity of taking measures was evaluated based on the assessment of the reported cases of adverse drug reactions for individual drug preparations rather than uniformly targeting injectable preparations containing arginine. This approach was taken because whether arginine itself can cause anaphylaxis was considered to be unclear at

present for the following reasons: An expert advisor expressed an opinion that the mechanism involving direct mast cell stimulation is only hypothetical; factors related to intravenous administration of hyperosmolar preparations may be involved; arginine is an amino acid that is biosynthesized in the human body.

At present, it is not clear whether arginine itself may cause anaphylaxis. However, for injectable preparations containing arginine as an excipient, cases involving anaphylaxis should be confirmed and evaluated as necessary in a similar way as described above, taking into account the description in the package inserts.

Reference: Number of cases*2 and patient mortalities involving anaphylaxis reported in Japan

a., c., d., f., g., i. to l., o. to q., t., v.

No cases have been reported to date.

b.

A total of 2 cases have been reported to date. (A causal relationship between the drug and the event was reasonably possible for these cases.)

No patient mortalities have been reported to date.

e.

A total of 6 cases have been reported to date. (A causal relationship between the drug and the event could not be established for any of these cases.)

A total of 4 patient mortalities have been reported to date. (A causal relationship between the drug and the death subsequent to the event could not be established for any of these cases.)

h.

A total of 3 cases have been reported to date (including 1 case for which a causal relationship between the drug and the event was reasonably possible).

No patient mortalities have been reported to date.

m.

One case has been reported to date. (A causal relationship between the drug and the event could not be established for this case.)

No patient mortalities have been reported to date.

n.

One case has been reported to date. (A causal relationship between the drug and the event could not be established for this case.)

No patient mortalities have been reported to date.

r.

A total of 4 cases have been reported to date (including 1 case for which a causal relationship between the drug and the event was reasonably possible).

No patient mortalities have been reported to date.

s.

A total of 6 cases*3 have been reported to date (including 1 case for which a causal relationship between the drug and the event was reasonably possible).

No patient mortalities have been reported to date.

u.

A total of 15 cases have been reported to date (including 4 cases for which a causal relationship between the drug and the event was reasonably possible).

A total of 3 patient mortalities have been reported to date. (A causal relationship between the drug and the death subsequent to the event could not be established for any of these cases.)

w.

A total of 2 cases have been reported to date (A causal relationship between the drug and the event was reasonably possible for 1 case, in which the drug was administered outside the approved indications).

No patient mortalities have been reported to date.

x.

A total of 8 cases have been reported to date (including 6 cases for which a causal relationship between the drug and the event was reasonably possible).

No patient mortalities have been reported to date.

*1Including cases submitted by the marketing authorization holders, which were reported prior to the start of registration in the PMDA's database for adverse drug reactions etc.

*2Cases collected in the PMDA's database for adverse drug reactions, etc. reports

*3Including 5 cases reported for a drug preparation whose marketing had been discontinued

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
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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).

Pharmaceuticals and Medical Devices Agency

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Attachment

	No.	Non-proprietary name	Brand name (marketing authorization holder)	Japanese market launch	Indications
Mixed amino acid preparations	a.	−	Moriamin-S Injection (AY Pharmaceuticals Co., Ltd.)	June 1960	Amino acid supplementation under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
	b.	−	Hy-Pleamin Injection-10% (Fuso Pharmaceutical Industries, Ltd.)	October 1960	Amino acid supplementation under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
	c.	−	Proteamin 12 Injection (Terumo Corporation)	March 1975	Amino acid supplementation under the following conditions: •When the patient has difficulty with protein intake or absorption due to conditions such as before/after surgery, gastrointestinal disorders, or being on a restricted diet •When the patient experiences substantial protein loss due to surgery, thermal burns, etc. •When the patient has hypoproteinaemia due to various diseases and poor oral intake •When the patient has substantial increases in wasting and demand for protein associated with febrile/wasting diseases, etc.
	d.	−	Moripron-F Injection (AY Pharmaceuticals Co., Ltd.)	January 1982	Amino acid supplementation under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
	e.	−	Aminoleban Injection (200 mL bag, 500 mL bag) (Otsuka Pharmaceutical Factory, Inc.)	March 1984	Improvement of encephalopathy during chronic liver disorder

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

	No.	Non-proprietary name	Brand name (marketing authorization holder)	Japanese market launch	Indications
	f.	−	Terufis I.V. Infusion (200 mL, 500 mL) (Terumo Corporation)	September 1999	Improvement of encephalopathy during chronic liver disorder
	g.	−	Hikarilevan Injection (200 mL soft bag, 500 mL soft bag) (Hikari Pharmaceutical Co., Ltd.)	December 2003	Improvement of encephalopathy during chronic liver disorder
	h.	−	Amiparen Injection (200 mL bag, 300 mL bag, 400 mL bag) (Otsuka Pharmaceutical Factory, Inc.)	May 1988	Amino acid supplementation under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
	i.	−	Aminic Injection (AY Pharmaceuticals Co., Ltd.)	June 1989	Amino acid supplementation under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
	j.	−	Morihepamin Intravenous Drip Injection (200 mL, 300 mL, 500 mL) (AY Pharmaceuticals Co., Ltd.)	January 1993	Improvement of encephalopathy during chronic liver disorder
	k.	−	Amizet B Infusion (Terumo Corporation)	January 1994	Amino acid supplementation under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
	l.	−	Pleamin-P Injection (Fuso Pharmaceutical Industries, Ltd.)	September 1995	Amino acid supplementation in neonates (weighing ≥ 2 kg at birth, in principle), babies, and infants aged 1-3 years in the following conditions:

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					Hypoproteinaemia, undernutrition state, before/after surgery
	m.	–	Kidmin Injection (200 mL bag, 300 mL bag) (Otsuka Pharmaceutical Factory, Inc.)	September 1996	Amino acid supplementation during acute and chronic renal failure under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
	n.	–	Neoamiyu Injection (AY Pharmaceuticals Co., Ltd.)	September 1996	Amino acid supplementation during acute and chronic renal failure under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
	o.	L-Lysine hydrochloride/ L-arginine hydrochloride	Lysakare Injection (Novartis Pharma K.K.)	September 2021	Reduction of renal exposure to lutetium (^{177}Lu) oxodotreotide
Mixed amino acid/sorbitol preparation	p.	–	Hy-Pleamin S Injection–10% (Fuso Pharmaceutical Industries, Ltd.)	October 1962	Amino acid supplementation under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
Mixed amino acid/glucose preparation	q.	–	Plas-Amino Injection (200 mL bag, 500 mL bag) (Otsuka Pharmaceutical Factory, Inc.)	September 1982	Amino acid supplementation under the following conditions: Hypoproteinaemia, undernutrition state, before/after surgery
Mixed amino acid/glucose/ inorganic salt preparations	r.	–	PNtwin Injection No-1, No-2, No-3 (AY Pharmaceuticals Co., Ltd.)	December 1993	Supplementation of water, electrolytes, amino acids, and calories when supplementation by oral or enteral nutrition is impossible or insufficient and total parenteral nutrition is the only option
	s.	–	Twinpal Injection (500 mL, 1,000 mL)	September 2004	Supplementation of amino acids, electrolytes, and water under the following conditions:

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			(AY Pharmaceuticals Co., Ltd.)		•When the patient has poor oral intake with mild hypoproteinaemia or mild undernutrition •Before/after surgery
Other preparations	t.	−	Paresafe Injection (AY Pharmaceuticals Co., Ltd.)	June 2006	Supplementation of amino acid, electrolyte, vitamin B_1, and water under the following conditions: •When the patient has poor oral intake with mild hypoproteinaemia or mild undernutrition •Before/after surgery
	u	−	Bfluid Injection (500 mL bag, 1,000 mL bag) (Otsuka Pharmaceutical Factory, Inc.)	June 2006	Supplementation of amino acid, electrolyte, vitamin B_1, and water under the following conditions: •When the patient has poor oral intake with mild hypoproteinaemia or mild undernutrition •Before/after surgery
v.		L-Arginine L-glutamate hydrate	Argimate Injection 10% (AY Pharmaceuticals Co., Ltd.)	December 1961	Hyperammonaemia
w.		L-Arginine hydrochloride	Argi-U Injection 20 g (AY Pharmaceuticals Co., Ltd.)	November 2000	An emergent decrease in blood ammonia concentration in acute aggravation of hyperammonaemia under the following conditions, when it cannot be controlled by oral preparations: Congenital urea cycle disorder [Carbamoylphosphate synthetase deficiency, ornitine transcarbamylase deficiency, argininosuccinate synthetase deficiency (citrullinaemia), argininosuccinate lyase deficiency (argininosuccinic aciduria)] or lysinuric protein intolerance
x.		L-Arginine hydrochloride	Arginine Injection “AY” 30 g	September 1981	This product is used for pituitary function tests. The normal response should be determined by individual

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	No.	Non-proprietary name	Brand name (marketing authorization holder)	Japanese market launch	Indications
			(AY Pharmaceuticals Co., Ltd.)		institutions, but normally the peak is reached at 60 to 120 minutes after the start of injection in normal patients, with a blood growth hormone level of 10 ng/mL measured by radioimmunoassay. However, it is preferable to repeat the test to make a decision if the pre-dose blood growth hormone level is low and the highest level does not exceed 5 ng/mL.

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