Revised: May 2022 (1st version)

Standard Commodity Classification No. of Japan:	873259

Storage: Store at room temperature.
Shelf Life: 12 months after production

Approval No.	22600AMX00527000
Date of Initial Marketing in Japan	May 2014

Enteral nutrient (for oral/enteral supplementation)

ENEVO® Liquid for Enteral Use

®Registered trademark (owner: Abbott Laboratories)

ENEVO®

2. CONTRAINDICATIONS

(This drug is contraindicated to the following patients.)

2.1 Patients with known hypersensitivity to the ingredients of ENEVO

2.2 Patients with milk protein allergy [A milk protein contained in ENEVO may cause shock or anaphylaxis.]

2.3 Patients with ileus [Such patients have intestinal transit disorder.]

2.4 Patients with no residual intestinal function [Water, electrolytes, nutrients, etc. are not absorbed in the intestine.]

2.5 Patients with severe hepatic or renal impairment [See 9.2.1 and 9.3.1.]

2.6 Patients with glucose metabolism abnormal, such as severe diabetes mellitus [Hyperglycemia, hyperketonemia, etc. may occur.]

2.7 Patients with inborn errors of amino acid metabolism [The symptoms of amino acid metabolism disorders, such as acidosis, vomiting, and consciousness disturbed, may occur.]

3. COMPOSITION AND PRODUCT DESCRIPTION

3.1 Composition

Ingredient Composition

Excipients	Stabilizers (Crystalline cellulose and Carmellose sodium), pH-adjusters (Potassium hydroxide and Citric acid hydrate), flavors (Vanillin, Ethylvanillin, and Propylene glycol)	
Calories	One milliliter of ENEVO contains 1.2 kcal.	
Active ingredients in each 250-mL can (300 kcal)	Milk Protein Isolate	12.6 g
	Whey Protein Concentrate	1.7 g
	Soy Protein Isolate	1.5 g
	High-Oleic Sunflower Oil	5.3 g
	Rapeseed Oil	2.2 g
	Medium Chain Fatty Acid Triglyceride	1.3 g
	Fish Oil	0.10 g
	Soybean Lecithin, S.B. Phosphatide	0.46 g
	Dextrin	26.8 g
	Sucrose	8.7 g
	Resistant Maltodextrin	3.5 g
	Fructo-Oligosaccharide	1.7 g
	Soybean Polysaccharide	0.30 g
	Retinol Palmitate	0.31 mg
	β-Carotene	0.16 mg
	Cholecalciferol	2.8 μg
	Tocopherol Acetate	12 mg
	Phytonadione	29 μg
	Ascorbic Acid	63 mg
	Thiamine Chloride Hydrochloride	0.57 mg
	Riboflavin	0.80 mg
	Pyridoxine Hydrochloride	0.94 mg
	Cyanocobalamin	0.88 μg
	Choline Chloride	0.25 g
	Folic Acid	68 μg
	Nicotinamide	4.5 mg
	Calcium Pantothenate	2.7 mg
	Biotin	13 μg
	Taurine	45 mg
	L-Carnitine	32mg
	Sodium Chloride	0.11 g
	Sodium Citrate Hydrate	0.79 g
	Potassium Chloride	0.25 g
	Potassium Citrate	0.48 g
	Magnesium Monohydrogen Phosphate	0.38 g
	Tribasic Calcium Phosphate	82 mg
	Ferrous Sulfate Hydrate	22 mg
	Zinc Sulfate Hydrate	20 mg
	Manganese (II) Chloride Tetrahydrate	4.9 mg
	Copper Sulfate	1.9 mg
	Chromium (III) Chloride Hexahydrate	0.16 mg
	Disodium Molybdate (VI) Dihydrate	85 μg
	Sodium Selenate	49 μg

Nutritional Composition

Nutrients in each 250-mL can (300 kcal)	Protein	13.5 g
	Fat	9.6 g
	Carbohydrate	39.6 g
	Fructo-Oligosaccharide	1.7 g
	Vitamin A	190 μgRE
	Vitamin D	2.8 μg
	Vitamin E	11 mg
	Vitamin K	29 μg
	Vitamin C	63 mg
	Vitamin B_1	0.51 mg
	Vitamin B_2	0.80 mg
	Vitamin B_6	0.77 mg
	Vitamin B_{12}	0.88 μg
	Choline	0.21 g
	Folic Acid	68 μg
	Niacin	4.5 mg
	Pantothenic Acid	2.5 mg
	Biotin	13 μg
	Taurine	45 mg
	L-Carnitine	32 mg
	Sodium	0.23 g
	Potassium	0.30 g
	Chloride	0.25 g
	Calcium	0.29 g
	Phosphorus	0.25 g
	Magnesium	52 mg
	Manganese	1.4 mg
	Copper	0.48 mg
	Zinc	4.5 mg
	Iron	4.4 mg
	Chromium	31 μg
	Molybdenum	34 μg
	Selenium	20 μg

Note: The sodium chloride equivalent per can (250 mL) of ENEVO is 0.586 g.

3.2 Product Description

Description	A brownish suspension
Odor	A characteristic aroma
Taste	Sweet
pH	6.1~7.0
Osmotic Pressure	ca. 350 mOsm/L

Specific Gravity	ca. 1.1
Viscosity	ca. 16 mPa·s

4. INDICATIONS

Generally, ENEVO is used to maintain the nutritional health of postoperative patients. It can be used for tube feeding, especially in patients who have difficulty in oral intake for a long period of time.

5. PRECAUTIONS CONCERNING INDICATIONS

The recovery of gastrointestinal motility, which allows patients to take fluid, should be confirmed before administering ENEVO after operation.

6. DOSAGE AND ADMINISTRATION

Usually, ENEVO should be administered to adults via a feeding tube or orally at a standard volume of between 1,000 and 1,667 mL (1,200 to 2,000 kcal) per day. When feeding via a tube, ENEVO should be administered at a rate of 62.5 to 104 mL (75 to 125 kcal) per hour continuously or intermittently by dividing the daily dose into several doses. If oral intake is possible, ENEVO may be orally administered once daily or in multiple divided doses.

Usually, however, ENEVO should be administered as an initial volume of 333 mL/day (400 kcal/day) at a lower rate (approximately 41.7 mL or less per hour [≤ 50 kcal per hour]). Thereafter, the volume of ENEVO should be gradually increased to the standard volume according to patient's condition. The dose, dosing concentration, and feeding rate should be adjusted, as appropriate, according to patient's age, body weight, and symptoms. Also consider diluting the drug formulation with water before administration, especially in the early stage of administration.

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

7.1 Once the patient becomes able to take sufficient nutrition by oral intake, switch from tube feeding to oral intake immediately.

7.2 The effectiveness of ENEVO administered for more than 2 weeks has not been confirmed in the clinical studies of ENEVO.

8. IMPORTANT PRECAUTIONS

8.1 Since patients may become deficient in vitamins, electrolytes (e.g., sodium), or trace minerals, they should be supplemented with vitamins, etc. as necessary.

8.2 Observe the patient carefully, especially in the early stage of administration. If any adverse reaction, such as diarrhoea, is observed, take appropriate measures, such as reducing the dose or discontinuing the administration of ENEVO.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.1 Patients with Complication or History of Diseases, etc.

9.1.1 Patients with short-bowel syndrome

Diarrhoea may be exacerbated.

9.1.2 Patients with pancreatitis acute

Pancreatitis may be exacerbated.

9.1.3 The following patients requiring careful monitoring of fluid balance

- Unconscious patients
- Patients who cannot complain of thirst
- Patients with severe fever
- Patients with significant dehydration, such as serious diarrhoea

These patients tend to lose their fluid balance.

9.2 Patients with Renal Impairment

9.2.1 Patients with severe renal disorder

Do not administer ENEVO. Azotemia and related symptoms may occur. [See 2.5.]

9.3 Patients with Hepatic Impairment

9.3.1 Patients with severe hepatic disorder

Do not administer ENEVO. Hepatic coma and related symptoms may occur. [See 2.5.]

9.4 Patients with Reproductive Potential

[See 9.5.1.]

9.5 Pregnant Women

9.5.1 Women during the first trimester of pregnancy or who wish to become pregnant

When ENEVO is administered, care should be taken regarding the dosage regimen, such as limiting the daily dose of vitamin A derived from ENEVO to less than 5,000 IU (1,500 μg of retinol equivalent [RE]) per day. An overseas epidemiological study[1)] has suggested an increased incidence of malformations, mainly in the cranial neural crest among neonates born from women who took 10,000 IU (3,000 μg RE) or more of vitamin A per day during the three months before pregnancy and the first trimester of pregnancy. [See 9.4.]

9.5.2 Pregnant women (except pregnant women during the first trimester)

ENEVO should be administered only when the therapeutic benefits are expected to outweigh the risks.

9.6 Breast-feeding Women

Considering the therapeutic and breast-feeding benefits, determine whether breast-feeding should be continued or discontinued.

9.7 Pediatric Use

No clinical study of ENEVO aiming to evaluate its efficacy or safety in children has been conducted.

9.8 Geriatric Use

ENEVO should be administered with attention to the dose, dosing concentration, and feeding rate. In general, the elderly often have reduced physiological function.

10. INTERACTIONS

10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Warfarin	The effect of warfarin may be reduced.	Phytonadione (vitamin K_1) antagonizes the effect of warfarin (ENEVO contains 29 μg of phytonadione per 250 mL).

11. ADVERSE REACTIONS

Since the following adverse reactions may occur, observe the patient carefully, and if any abnormality is observed, take appropriate measures, such as discontinuing the administration of ENEVO.

11.1 Clinically Significant Adverse Reactions

11.1.1 Shock, anaphylaxis (unknown incidence for both)

In the event of blood pressure decreased, consciousness disturbed, dyspnoea, cyanosis, nausea, chest distress, facial flushing, itching, sweating, etc., discontinue ENEVO administration immediately, and treat the patient appropriately.

11.2 Other Adverse Reactions

	≥ 5%	0.1 to < 5%
Gastrointestinal	Diarrhoea (40.7%), Constipation (15.3%), Abdominal distension (10.2%), Abdominal pain	Ascites, Nausea, Portal venous gas
Metabolism/ Nutrition	Hyponatraemia, Hyperkalaemia	
Liver		Hepatic function abnormal

Respiratory		Chylothorax
Blood	Gamma-glutamyltransferase increased, Blood alkaline phosphatase increased	Blood potassium increased, Alanine aminotransferase increased, Blood glucose increased, Eosinophil count increased, Liver function test abnormal
Urine		Urine output decreased

Note: Take appropriate measures, such as reducing the dose, feeding rate, or dosing concentration, or discontinuing the administration.

14. PRECAUTIONS CONCERNING USE

14.1 Precautions Concerning Administration of the Drug

14.1.1 The use of an enteral feeding set or feeding tube, etc. made of polyvinyl chloride containing di-(2-ethylhexyl) phthalate (DEHP) as a plasticizer will cause elution of DEHP into the drug formulation. Therefore, it is advisable that a DEHP-free feeding set and feeding tube, etc. should be used to administer ENEVO.

14.1.2 ENEVO is an enteral nutrient. Do not administer ENEVO intravenously.

14.1.3 Check gastric residuals at the start of intermittent feeding or every several hours during continuous feeding.

14.1.4 For tube feeding, flush the feeding tube with a small amount of water at the end of intermittent feeding or every several hours during continuous feeding.

14.1.5 Shake the can immediately before opening it to use ENEVO.

14.1.6 When warming the drug formulation, it is advisable to warm it in the unopened can by immersing in warm water (30 to 40°C). Avoid heating the can over an open flame.

17. CLINICAL STUDIES

17.1 Clinical Studies for Efficacy and Safety

17.1.1 Japanese phase 3 comparative study

In the phase 3 comparative study, ENEVO or a comparator was administered for 10 days (from postoperative day 3 to postoperative day 12) to patients who underwent esophageal cancer surgery or total gastrectomy due to gastric cancer and required tube feeding for the maintenance of nutritional health due to difficulty in sufficient oral food intake. The ENEVO group consisting of 59 safety-evaluable subjects and the control group showed similar changes over time in the primary endpoint of rapid turnover protein (RTP).[2)]

Adverse reactions were reported in 43 (72.9%) of the 59 safety-evaluable subjects. Common adverse reactions were gastrointestinal symptoms, including diarrhoea (n = 24; 40.7%), constipation (n = 9; 15.3%), abdominal distension (n = 6; 10.2%), and abdominal pain (n = 5; 8.5%), as well as hyponatraemia (n = 4; 6.8%) and hyperkalaemia (n = 3; 5.1%). Common laboratory abnormalities were γ-glutamyltransferase increased (n = 5; 8.5%) and blood alkaline phosphatase increased (n = 4; 6.8%).

18. PHARMACOLOGY

18.1 Mechanism of Action

ENEVO is effective for supplementation of protein, carbohydrate, lipid, electrolytes, energy, vitamins, minerals, and water.

18.2 Protein

18.2.1 Milk protein (whey protein and cow's milk protein) and soybean protein isolate are blended as protein sources of ENEVO in a ratio of 90.5:9.5, considering their amino acid complementary effects and the efficient utilization of amino acids, and 250 mL of ENEVO contains 13.5 g of protein (energy composition: 18%).

18.2.2 Non-protein calorie/nitrogen ratio (NPC/N ratio) of ENEVO is 116 (based on analysis values).

18.3 Carbohydrate

The major carbohydrate sources of ENEVO are dextrin and sucrose, and 250 mL of ENEVO contains 39.6 g of carbohydrate (energy composition: 53%).

18.4 Lipid

18.4.1 The major lipid sources of ENEVO are high-oleic sunflower oil, rapeseed oil, and medium chain fatty acid triglyceride, and 250 mL of ENEVO contains 9.6 g of lipid (energy composition: 29%).

ENEVO is a uniform, stable, fine-particle suspension, and is thus readily digestible.

18.4.2 ENEVO contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derived from fish oil. Thus, ENEVO contains omega-3, -6, and -9 fatty acids in a well-balanced manner.

18.5 Water

ENEVO contains 203 mL of water in a 250-mL volume.

20. PRECAUTIONS FOR HANDLING

20.1 Avoid keeping ENEVO in a freezer or at a high temperature above room temperature.[3)]

20.2 Once opened, unused ENEVO should be kept away from direct sunlight and used up as soon as possible to prevent microbial contamination. If it is kept in a refrigerator for unavoidable reasons, it should be tightly resealed and used within 48 hours after opening.[3)]

20.3 In case any abnormality is found in the drug formulation due to breakage of the container, etc., do not use it.

22. PACKAGING

24 cans [250 mL (can) × 24]

23. REFERENCES

1) Rothman KJ, et al. *The New England Journal of Medicine*. 1995; 333 (21): 1369
2) Fukushima R, et al. *Journal of Japanese College of Surgeons*. 2014; 39: 840
3) Abbott Japan LLC (data on file). Data on stability (approved on March 24, 2014).

24. REFERENCE REQUEST AND CONTACT INFORMATION

Abbott Japan LLC Customer Service
3-5-27, Mita, Minato-ku, Tokyo 108-6305
Toll-free number: 0120-964-930

26. MARKETING AUTHORIZATION HOLDER, etc.

26.1 Marketing Authorization Holder

Abbott Japan LLC
3-5-27, Mita, Minato-ku, Tokyo