

Revised: June 2009 (11th version)

Standard Commodity Classification No. of Japan
87219

- Microcirculation activator -
Juvela N[®] Capsules 100mg
Juvela N[®] Soft Capsules 200mg
Juvela N[®] Fine Granules 40%
 <Tocopherol nicotinate preparation>

Storage	Capsules 100mg	Soft Capsules 200mg	Fine Granules 40%
1) JUVELA N should be stored at room temperature. 2) PTP packaged soft capsules should be protected from high temperature and moisture after opening aluminum bag, and bottled capsules should be protected from high temperature and moisture after opening cap. (Capsule shells may be softened.)	21800AMX10555000	21800AMX10556000	21800AMX10557000
	Dec 2006	Dec 2006	Dec 2006
	Jan 1967	Jul 1984	Jul 1984
	Date of latest reexamination Sep 1999		

Expiration date
JUVELA N should be used before the expiration date indicated on the package or label.

Caution – Soft capsules should be protected from high temperature and high humidity to be prepared and administered for a long period of time (Capsule shell may cause adhesion.).

DESCRIPTION

1. Composition

Capsules 100mg:

Each opaque red and white hard capsule contains 100 mg of tocopherol nicotinate.

It also contains FD&C Yellow No.6 (Sunset Yellow-FCF), hydrated silicon dioxide, light anhydrous silicic acid, microcrystalline cellulose, FD&C Blue No.1 (Brilliant Blue-FCF), FD&C Red No.3 (Erythrosine), gelatin, talc, macrogol 6000, methylcellulose and sodium lauryl sulfate as inactive ingredients.

Soft capsules 200mg:

Each orange soft capsule contains 200 mg of tocopherol nicotinate.

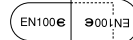
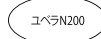
It also contains L-aspartic acid, FD&C Yellow No.6 (Sunset Yellow - FCF), carnauba wax, glycerol esters of fatty acids, titanium oxide, gelatin, D-sorbitol solution, medium chain fatty acid triglyceride, concentrated glycerin, ethyl parahydroxybenzoate and propyl parahydroxybenzoate as inactive ingredients.

Fine granules 40%:

Each gram of white to light yellowish white fine granules contains 400 mg of tocopherol nicotinate.

It also contains microcrystalline cellulose, macrogol 6000, D-mannitol, hydrated silicon dioxide and methylcellulose as inactive ingredients.

2. Product description

Brand name	Dosage form and identification code	Appearance	Description
JUVELA N Capsules 100mg	Hard Capsules		Capsules Cap: Opaque red Body: White Contents White to light yellowish white granules or powder
	EN100E	Length (mm) 16.2	Weight (mg) 257
JUVELA N Soft Capsules 200mg	Soft Capsules		Capsules Orange Contents Yellowish white, viscous suspension or semisolid
	—*	Long diameter (mm) 14.7	Short diameter (mm) 7.2
JUVELA N Fine Granules 40%	Fine Granules		White to light yellowish white

* The term of “ユベラN200” is printed on the surface of each soft capsule.

INDICATIONS

Accompanying symptoms resulting from the following

Hypertension

Hyperlipidemia

Peripheral circulatory disturbance resulting from the following

Arteriosclerosis obliterans

DOSAGE AND ADMINISTRATION

Capsules 100mg:

The usual adult dosage for oral use is 300 - 600 mg of tocopherol nicotinate (3 - 6 capsules) daily in three divided doses.

The dosage may be adjusted depending on the patient's age and symptoms.

Soft capsules 200mg:

The usual adult dosage for oral use is 3 capsules daily in three divided doses.

The dosage may be adjusted depending on the patient's age and symptoms.

The usual adult dosage of tocopherol nicotinate for oral use is 300 - 600 mg daily in three divided doses.

Fine granules 40%:

The usual adult dosage for oral use is 300 - 600 mg of tocopherol nicotinate (0.75 - 1.5 g of fine granules) daily in three divided doses.

The dosage may be adjusted depending on the patient's age and symptoms.

PRECAUTIONS**1. Adverse Reactions**

Adverse reactions were reported in 105 of 5,621 patients (1.87%). (Sum of the clinical trials)

	5% > ≥0.1%	<0.1%	Incidence unknown
Gastrointestinal	Anorexia, stomach discomfort, stomachache, nausea, diarrhea and constipation		
Hypersensitivity ^{note)}		Rash	
Hepatic		Liver Dysfunction (Elevation of AST (GOT) and ALT (GPT), etc.)	
Others		Feeling of warmth, flushing	Facial edema, edema

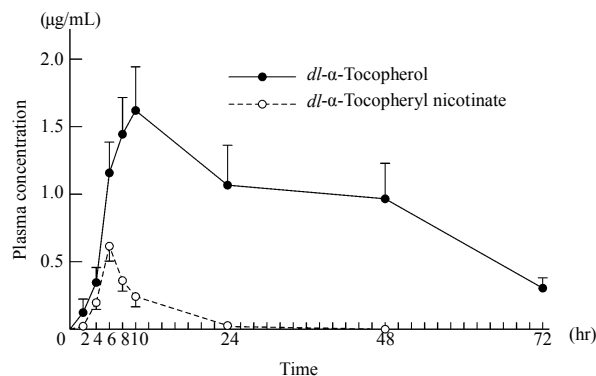
Note) In the event of such symptoms, treatment should be discontinued or other appropriate measures taken.

2. Precautions concerning Use

Caution in handing over drug (capsules and soft capsules)
For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in serious complications such as mediastinitis.]

PHARMACOKINETICS**1. Blood concentrations**

Tocopherol nicotinate was administered orally to 12 healthy adult male volunteers at a single dose of 600 mg ^{note)} after a meal, and plasma concentrations of tocopherol nicotinate (the unchanged drug) and tocopherol were determined. The plasma peak concentration ($C_{max}=0.615 \mu\text{g/mL}$) of the unchanged drug was reached 6 hr after administration, and thereafter declined rapidly with an elimination half-life of 4.3 hr. The peak plasma tocopherol concentration (except endogenous tocopherol) ($C_{max}=1.62 \mu\text{g/mL}$) was reached 10 hr after administration and declined gradually with an elimination half-life of 38.5 hr.¹⁾



Plasma unchanged drug and α -tocopherol concentration after administration of tocopherol nicotinate

(Mean \pm S.E., n=12)

2. Effect of meal

When tocopherol nicotinate was administered orally to 4 healthy adult male volunteers at a single dose of 600 mg ^{note)}, the peak plasma concentration was 32 times higher and the AUC was 29 times larger after a meal than during fasting. The absorption of tocopherol nicotinate is significantly influenced by food intake.²⁾

Note: A single dose of 600 mg is unapproved.

CLINICAL STUDIES

Clinical efficacy

1. Hypertension

In double-blind and open labeled clinical trials, it has been shown that tocopherol nicotinate alleviates symptoms associated with hypertension. Improvement was noted, particularly with regard to symptoms such as numbness of the hands and feet, feeling of dizziness, neck and shoulder stiffness, headache, insomnia, tinnitus, shortness of breath, depression and feeling of coldness in the extremities.^{3, 4)}
In a comparative clinical trial with 40 elderly patients complaining of coldness or numbness in the extremities due to hypertension etc., improvement produced by tocopherol nicotinate was moderate to remarkable as seen by thermographic photographs and thermographic distribution histograms in 60% (12/20), and while there was fair to remarkable improvement in all patients.⁵⁾

2. Hyperlipidemia

In open labeled clinical trials, it has been shown that statistically significant reduction for the patients of high total cholesterol before administrations, and shown that significant increase for the patients of low HDL-cholesterol before administrations. And statistically significant reduction in serum lipid peroxides was observed in patients with hyperlipidemia.⁶⁾

3. Peripheral circulatory disturbances

In double-blind and open labeled clinical trials, tocopherol nicotinate has been demonstrated to be useful in patients with peripheral circulatory disturbances such as arteriosclerosis obliterans.

PHARMACOLOGY

1. Improvement of lipid metabolism

- (1) In aged or cholesterol-loaded rats, tocopherol nicotinate decreases serum total cholesterol concentrations by increasing the turnover rate of cholesterol, which is considered to be due to enhanced catabolism/excretion of cholesterol. Tocopherol nicotinate also decreases lipid peroxide and triglyceride concentrations.^{7,8)}
- (2) Tocopherol nicotinate decreases total serum cholesterol and triglyceride levels in humans, while it increases the serum levels of high-density lipoprotein (HDL) cholesterol in lipoprotein metabolism.⁶⁾

2. Enhancement of microcirculation

- (1) In an experiment with unanesthetized rabbits, tocopherol nicotinate has been demonstrated to maintain vasomotion and increase peripheral blood flow in the ear conchae by directly acting on the blood vessel walls, not via the nervous system.⁹⁾
- (2) In a clinical trial, tocopherol nicotinate is more significantly effective in alleviating peripheral circulatory disturbances than coadministration of vitamin E and nicotinic acid.¹⁰⁾

3. Strengthening of blood vessels

Tocopherol nicotinate mitigates capillary hyperpermeability in humans and decreases the number of purpura spots.¹¹⁾

4. Inhibition of platelet aggregation

- (1) Tocopherol nicotinate inhibits the aggregation induced by epinephrine, arachidonic acid, collagen and ADP in stimulated human platelets.¹²⁾
- (2) Tocopherol nicotinate is more potent than tocopherol and tocopherol acetate in inhibiting the aggregation induced by arachidonic acid and collagen in human platelet-rich plasma.¹³⁾

5. Restoration of arterial oxygen partial pressure

Tocopherol nicotinate restores the decreased partial pressure of oxygen in human arterial blood.¹⁴⁾

PHYSICOCHEMISTRY

Nonproprietary name:

Tocopherol Nicotinate (JAN)

dl- α -Tocopheryl Nicotinate (Another name)

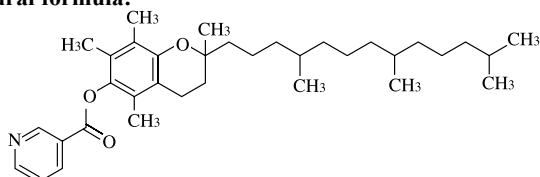
Chemical name:

2, 5, 7, 8-Tetramethyl-2-(4, 8, 12-trimethyltridecyl) chroman-6-yl nicotinate

Molecular formula: C₃₅H₅₃NO₃

Molecular weight: 535.80

Structural formula:



Description:

Tocopherol Nicotinate occurs as yellow to orange-yellow liquid or solid. It is freely soluble in ethanol (99.5), and practically insoluble in water. A solution of Tocopherol Nicotinate in ethanol (99.5) (1 in 10) shows no optical rotation. It is affected by light.

PACKAGING

JUVELA N Capsules 100mg:

Boxes of 100, 210 (21 Caps.×10), 1,000 and 1,050 (21 Caps.×50) in press-through packages, and bottles of 500

JUVELA N Soft capsules 200mg:

Boxes of 100, 210 (21Caps. × 10), 1,000 and 1,050 (21 Caps. × 50) in press-through packages, and bottles of 500

JUVELA N Fine granules 40%:

Bottles of 100g

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REQUEST FOR LITERATURE SHOULD BE MADE TO:

Safety Management Department

Fax: 03-3811-2710

Eisai Co., Ltd.

REQUEST FOR PRODUCT INFORMATION SHOULD BE MADE TO:

Customer Information Service

Free Dial: 0120-419-497

Eisai Co., Ltd.

Manufactured and marketed by:

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BRAND NAMES IN OTHER COUNTRIES

Hijuven (Malaysia, Thailand)