

Revised: September 2009 (8th version)

Standard Commodity Classification No. of Japan
87316

- Hemostatic mechanism activating vitamin -
Kaytwo[®] N for Intravenous Injection 10mg

<Menatetrenone preparation>

Prescription drug

Storage
KAYTWO N should be stored in the LPE pack (Light Protect Easy open pack) at room temperature (If ampules are not kept in the LPE pack, the menatetrenone will be decomposed by light decreasing its content).

Approval No.	22100AMX00454000
Date of listing in the NHI reimbursement price	Sep 2009
Date of initial marketing in Japan	Aug 1991
Date of latest approval of indications	Mar 2002

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

Caution : Use only as directed by a physician.

CONTRAINDICATIONS (KAYTWO N is contraindicated in the following patients.)
 Patients with a history of hypersensitivity to KAYTWO N

DESCRIPTION

KAYTWO N is a light yellow, translucent injection contained in brown ampules (one-point-cut type). Each ampule of KAYTWO N contains following ingredients.

		Content (mg) per ampule (2mL)
Active ingredient	Menatetrenone	10
	Sesame oil	4
Inactive ingredients	Sodium hydroxide	q. s.
	Purified soybean lecithin	16
	D-Sorbitol	100
	Taurine	6
	Concentrated glycerin	100
Product description	KAYTWO N injection is a light yellow, translucent liquid.	
pH	6.0-8.0	
Osmotic pressure ratio	about 3 (ratio relative to isotonic chloride solution)	

INDICATIONS

The following diseases and symptoms caused by vitamin K deficiency:

- Hypoprothrombinemia caused by biliary atresia/biliary hyposecretion
- Neonatal hypoprothrombinemia
- Intrapartum hemorrhage
- Hypoprothrombinemia during coumarin anticoagulant therapy
- Hypoprothrombinemia due to poisoning by coumarin derivative rodenticides.

- <Precautions>

Warfarin, fumarin, coumatetralyl, bromadiolone, diphacinone and chlorophacinone are rodenticides known to cause hypoprothrombinemia in humans by its vitamin K antagonism. When KAYTWO N is used for the poisoned patient, it should be confirmed by blood coagulation tests that the poisoning is due to the anticoagulant effect of such rodenticides.

DOSAGE AND ADMINISTRATION

1. Hypoprothrombinemia caused by biliary atresia/biliary hyposecretion, intrapartum hemorrhage and hypoprothrombinemia during coumarin anticoagulant therapy.
 The usual adult dosage for intravenous administration is 10 - 20 mg of menatetrenone once daily.
2. Neonatal hypoprothrombinemia
 1-2 mg of menatetrenone should be administered intravenously once immediately after birth. Another 2 - 3 doses may be administered intravenously depending on the patient's condition.
3. Hypoprothrombinemia due to poisoning by coumarin derivative rodenticides.
 The single dosage for intravenous administration is 20 mg of menatetrenone. The dosage may be increased to 40 mg daily depending on symptoms and results of blood coagulation tests.

PRECAUTIONS

1. **Careful Administration (KAYTWO N should be administered with care in the following patients.)**
 - (1) Patients with a personal or familial predisposition to allergic reactions such as bronchial asthma, rash or urticaria.
 - (2) Patients with a history of drug hypersensitivity

2. Important Precautions

- (1) KAYTWO N must only be administered for abnormal vitamin K-dependent coagulation factors.
- (2) The administration of KAYTWO N should only be considered if no efficacy can be expected from an oral vitamin K preparation.
- (3) KAYTWO N should be administered to neonatal hypoprothrombinemia patients who have Thrombotest values of 20% or less or Hepaplastintest values of 30% or less.
- (4) Since KAYTWO N is effective in supplying vitamin K for patients with bleeding tendency due to vitamin K deficiency, the following cautions should be exercised.
 - 1) Since KAYTWO N is ineffective for hemostasis in patients without a vitamin K deficiency, it should not be administered to them.
 - 2) As a general rule, the following should be conducted: Measurement of prothrombin time, Thrombotest or Hepaplastintest, test for presence of PIVKA (protein induced by vitamin K absence or antagonist) and check for abnormal vitamin K-dependent coagulation factors. In the case of continuous administration of KAYTWO N, these tests should be conducted periodically.
 - 3) Since supplying vitamin K is ineffective for hemostasis in patients with coagulation disorders due to liver cell disorders such as hepatic cirrhosis, KAYTWO N should not be administered to them.
 - 4) Since KAYTWO N only becomes effective at 3 hr after administration, it should be kept in mind that an immediate effect can not be expected.
- (5) When a serious hemorrhagic event occurs, appropriate measures should be taken, such as giving a transfusion of fresh frozen plasma with KAYTWO N.
- (6) Patients should be carefully interviewed to see if they have a history of allergy or drug hypersensitivity before administration.
- (7) The patient's condition should be carefully monitored after injecting a small amount at the beginning of treatment. In the event of abnormal symptoms, treatment should be immediately discontinued.
- (8) The administration of KAYTWO N should be continued even if coagulation status recovers temporally, because some of the coumarin derivative rodenticide effects are long lasting. Treatment with it and blood coagulation tests should be continued till coagulation status recovers completely.

3. Drug Interactions

Precautions for coadministration (KAYTWO N should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Coumaric anticoagulant Warfarin potassium	It should be administered concomitantly with care.	KAYTWO N decreases the effect of warfarin.

4. Adverse Reactions

Adverse reactions were reported in 3 of 424 patients (0.71%). (At the end of special surveys on neonatal hypoprothrombinemia)

(1) Hypersensitivity

Rash (5% > $\geq 0.1\%$) may occur. In the event of such symptoms, treatment should be discontinued.

(2) Other

It has been reported that shock occurred due to a conventional menatetrenone injection, so the patient's condition should be carefully observed. In the event of any abnormal symptoms, treatment should be discontinued and appropriate measures taken.

5. Precautions concerning Use

(1) Rate of administration

Since rapid administration of KAYTWO N may cause shock, it is advisable to use intravenous drip infusion. In the case of intravenous administration, the drug should be injected gradually.

(2) Precaution during administration

In the case of intravenous drip infusion, a light-resistant cover should be used to avoid the photolysis of menatetrenone.

(3) Preparation

1) In the case of a drip infusion, KAYTWO N should be diluted with isotonic sodium chloride solution, JP or 5 % glucose injection, and administered continuously using a single infusion line.

2) KAYTWO N uses purified soybean lecithin as a solubilization agent. Combination with other drugs may reduce its solubilization capacity and cause changes of compatibility, so that if a final filter is used for drip infusion, it may become clogged quicker than normal.

3) Since KAYTWO N may cause changes of compatibility with plasma expanders (preparations including dextran, etc.) or heparin, it should not be mixed with them.

(4) Opening the ampule

KAYTWO N is supplied as one-point-cut ampules. The cut point of the ampule should be wiped with an alcohol swab before opening.

(5) Other

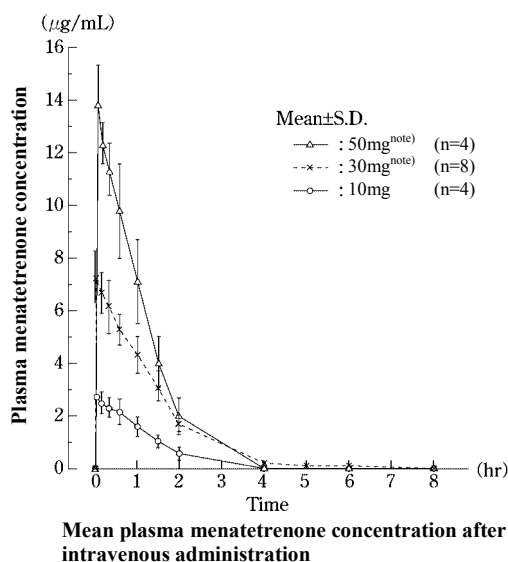
When a transfusion set made of polyvinyl chloride is used for this product, one that does not contain di-(2-ethylhexyl) phthalate (DEHP) as a plasticizer is recommended, due to the possibility of DEHP being eluted into this product.

PHARMACOKINETICS

Blood concentration

When KAYTWO N for Intravenous Injection 10mg was administered intravenously to healthy adult male volunteers at single doses of 10 (4 men), 30 (8 men) or 50^{note)} mg (4 men) of menatetrenone, the plasma menatetrenone concentration increased in proportion to dose. At a dose of 10 mg of menatetrenone, the mean plasma concentration was 2.76

$\mu\text{g/mL}$ at 6 min after administration, and thereafter, declined linearly and was $0.57 \mu\text{g/mL}$ at 2 hr after administration. The plasma concentration decreased in a biphasic pattern, and the mean half lives of 4 cases were 0.71 hr at the α phase and 17.52 hr at the β phase. AUC up to 48 hr after administration was $3.90 \mu\text{g} \cdot \text{hr/mL}$.



Note) Doses of 50 mg are unapproved.

Pharmacokinetic parameters after intravenous administration of menatetrenone

Dose (mg)	$t_{1/2\alpha}$ (hr)	$t_{1/2\beta}$ (hr)	AUC ₀₋₄₈ ⁸⁾ ($\mu\text{g/hr/mL}$)
10	0.71	17.52	3.90

CLINICAL STUDIES

Clinical efficacy

1. Hypoprothrombinemia caused by biliary atresia / biliary hyposecretion

When KAYTWO N for Intravenous Injection 10mg or vitamin K₂ injection (including polyoxyethylene hydrogenated castor oil 60) was administered to patients with hypoprothrombinemia resulting from biliary atresia or biliary secretion failure at a dose of 10 mg/day of menatetrenone for 7 days and their clinical efficacy was compared in a double-blind controlled clinical trial, there was found to be no significant difference between them in terms of improvement rate¹⁾

2. Neonatal hypoprothrombinemia

In a special survey to evaluate efficacy for neonatal hypoprothrombinemia targeting 53 patients (patients in whom at least one parameter was outside the normal range in a blood coagulation test conducted prior to administration), of 27 patients showing hemorrhage prior to administration, improvement was achieved in 26 (96%). A global improvement evaluation based on remission of hemorrhage and improvement in blood coagulation test over time indicated improvement in 28 of the 53 patients (53%).²⁾

3. Hypoprothrombinemia due to poisoning by coumarin derivative rodenticides

Outside of Japan it has been reported, that patients suffering from poisoning due to coumarin derivative rodenticides, recovered when given vitamin K.^{3, 4)}

PHARMACOLOGY

1. Mechanisms of action

Vitamin K₂ (K₂) is involved in the carboxylation reaction which converts the glutamic acid residues into physiologically active γ -carboxyglutamic acid in the biosynthesis process of the blood coagulation factors (prothrombin, VII, IX and X). Vitamin K₂ physiologically causes hemostasis by accelerating the synthesis of normal prothrombin, etc. in the liver and activating the hemostatic mechanism.⁵⁾

2. Improvement of hypoprothrombinemia

- (1) The ameliorating effect of the intravenous administration of 5 mg of K₂ or vitamin K₁ (K₁) for warfarin potassium induced hypoprothrombinemia in isolated rabbit livers was examined. K₂ improved the prothrombin time of rabbit blood more rapidly than K₁, and in this respect, K₂ was 3 times stronger than K₁ at 1 hr and twice as strong at 2 hr after administration.⁶⁾
- (2) In two groups of rats, bleeding time was prolonged greatly, in one group, through an increased bleeding tendency due to dicoumarol (20 mg/kg) induced impairment of coagulation features and in the other by inducing hepatic function disorder using carbon tetrachloride (0.1 mL/kg). When K₂ was administered intramuscularly to these rats at a dose of 10mg/kg, in both groups the bleeding time was significantly shortened at 3 - 4 hr after administration ($p < 0.05$).⁷⁾

3. Comparison with Vitamin K2 Injection (including poly-oxyethylene hydrogenated castor oil 60)

The efficacy of KAYTWO N for Intravenous Injection 10mg was compared with vitamin K₂ injection in rats with warfarin potassium induced hypoprothrombinemia. KAYTWO N or vitamin K₂ Injection was administered intravenously to the rats at doses of 0.008, 0.04, 0.2 and 1.0 mg/kg of menatetrenone or they received a placebo, and the blood coagulation activity at 1, 3 and 6 hr after administration was examined using a Hepaplastintest. Efficacy against time was virtually the same for each dose of both preparations as were the dosage-activity curves for 1, 3 and 6 hr after administration of preparations.⁸⁾

PHYSICOCHEMISTRY

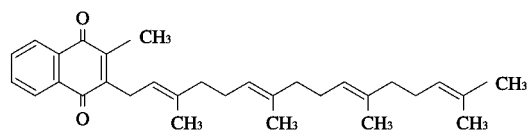
Nonproprietary name: Menatetrenone (JAN, INN)

Chemical name:

2-Methyl-3-[(2E, 6E, 10E)-3, 7, 11, 15-tetramethylhexadeca-2, 6, 10, 14-tetraen-1-yl]-1, 4-naphthoquinone

Molecular formula: C₃₁H₄₀O₂

Molecular weight: 444.65

Structural formula:**Description:**

Menatetrenone occurs as yellow crystals, crystalline powder, waxy mass or oily substance.

It is very soluble in hexane, soluble in ethanol (99.5), sparingly soluble in 2-propanol, slightly soluble in methanol, and practically insoluble in water.

It decomposes in light, and darkens.

Melting point: about 37°C

PRECAUTIONS FOR HANDLING

KAYTWO N is packaged in LPE pack to ensure quality during storage. The LPE pack should be opened immediately before using.

PACKAGING

KAYTWO N for Intravenous Injection 10mg (2 mL):

Boxes of 10 and 50 ampules

REFERENCES

- 1) Koyama K. et al.: J. New Remed. Clin, **38**, 1434, 1989.
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- 3) Chua J. D. et al.: Arch. Intern. Med., **158**, 1929, 1998.
- 4) Sittert N. J. et al.: Toxicology, **91**, 71, 1994.
- 5) Stenflo J. et al.: Proc. Natl. Acad. Sci. USA, **71**, 2730, 1974.
- 6) Hasegawa H. et al.: J. Clin. Exp. Med., **78**, 73, 1971.
- 7) Tajima T. et al.: Folia pharmacol. japon., **67**, 478, 1971.
- 8) Akiyama Y. et al.: Clin. Report, **23**, 3131, 1989.

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Fax: 03-3811-2710

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Customer Information Service

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