

Revised: November 2009 (9th version)

Standard Commodity Classification No. of Japan
87316

- Vitamin K₂ Preparation for Treatment of Osteoporosis -**Glakay[®] Capsules 15mg**

< Menatetrenone preparation >

Storage
GLAKAY should be stored at room temperature. PTP packages should be protected from high temperature and moisture after opening aluminum bag, and bottle packages should be protected from high temperature and moisture after opening cap. (Softening, discolor, and adhesion to the inside of press-through package may occur to capsule shells.)

Approval No.	20700AMZ00525000
Date of listing in the NHI reimbursement price	Aug 1995
Date of initial marketing in Japan	Oct 1995
Date of latest reexamination	Jun 2009
International birth date	Jul 1972

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

CONTRAINDICATIONS (GLAKAY is contraindicated in the following patients.)

Patients on warfarin potassium therapy
[See "Drug Interactions" section.]

DESCRIPTION**1. Composition**

Each soft orange capsule contains 15 mg of menatetrenone. It also contains L-aspartic acid, FD&C Yellow No.6 (Sunset Yellow - FCF), carnauba wax, hydrogenated oil, titanium oxide, gelatin, D-sorbitol solution, concentrated glycerin, ethyl parahydroxybenzoate, propyl parahydroxybenzoate, propylene glycol esters of fatty acid and glyceryl monooleate as inactive ingredients.

2. Product description

Brand name	Dosage form and identification code	Appearance	Description				
GLAKAY Capsules 15 mg	Soft Capsules	(グラケー)	Capsules: orange Content: light yellowish viscous liquid or semi-solid substance				
	—*	<table border="1"> <tr> <td>Long diameter (mm)</td> <td>Short diameter (mm)</td> <td>Weight (mg)</td> </tr> <tr> <td>9.6</td> <td>5.6</td> <td>190</td> </tr> </table>		Long diameter (mm)	Short diameter (mm)	Weight (mg)	9.6
Long diameter (mm)	Short diameter (mm)	Weight (mg)					
9.6	5.6	190					

* The term of "グラケー" is printed on the surface of each soft capsule.

INDICATIONS

Improvement of decrease in bone mass and relief of pain in patients with osteoporosis

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 45 mg of menatetrenone daily in three divided doses after meals.

PRECAUTIONS**1. Important Precautions**

(1) GLAKAY should be administered to patients who have been diagnosed as having osteoporosis and have a decrease in bone mass and pain, in accordance with the criteria prepared by the General Study Group on Pre-

vention and Treatment of Senile Osteoporosis (general criteria based on whether a decrease in bone mass, fracture and low back pain, etc. are present or not) of the Ministry of Health and Welfare (MHW) of Japan, etc.

(2) Rash, redness, pruritus or other symptoms may occur.

In the event of such symptoms, treatment should be discontinued.

2. Drug Interactions

Contraindications for coadministration (GLAKAY should not be coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Warfarin potassium. (WARFARIN)	Effect of warfarin may be diminished. If patients must use warfarin, it should prefer warfarin therapy and discontinue administration of GLAKAY. Blood coagulation test such as the prothrombin time and Thrombotest, should be conducted, and coagulability monitored periodically until the maintenance dose of warfarin has been reached.	Warfarin exhibits an anticoagulant action and prophylactic action against thrombosis by inhibiting the metabolic cycle of vitamin K in the liver cell and producing non-coagulant blood coagulation factors. GLAKAY is a vitamin K ₂ preparation and diminishes the action of warfarin when coadministered with it.

3. Adverse Reactions

Adverse reactions were reported in 302 of 6,321 patients (4.78%). (at the end of the reexamination period)

	5% > ≥0.1%	<0.1%	Incidence unknown
Gastrointestinal	Stomach discomfort, abdominal pain, diarrhea, nausea, stomatitis, anorexia, dyspepsia and constipation	Thirst, glossitis and vomiting	
Hypersensitivity	Rash and pruritus	Redness	
Psychoneurologic	headache	Dizziness, light-headedness and numbness	
Cardiovascular		Increase in blood pressure and palpitations	
Hepatic	Elevation of AST (GOT), ALT (GPT) and γ-GTP, etc.		

	5% > ≥0.1%	<0.1%	Incidence unknown
Urinary	Elevation of BUN, etc.		Urinary frequency
Others	Edema	Eye abnormalities and arthralgia	Malaise

4. Use in the Elderly

As GLAKAY is usually administered to the elderly for a long period of time, their condition should be carefully observed during administration.

5. Use during Pregnancy, Delivery or Lactation

The safety of GLAKAY in pregnant women or nursing mothers has not been established (no clinical experience).

6. Pediatric Use

The safety in children has not been established (no clinical experience).

7. Precautions concerning Use

(1) Caution in administration

GLAKAY should be taken after meals because its absorption is decreased when administered to patients with an empty stomach.

The absorption of GLAKAY decreases if a meal has a low fat content, since menatetrenone is lipophilic. [See "Pharmacokinetics" section.]

(2) Caution in handing over drug

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 concentration

GLAKAY was administered orally to 9 healthy adult male volunteers at a dose of one capsule (15 mg of menatetrenone) after a meal. The mean plasma menatetrenone concentration began to increase following a time lag of 1 hr after administration and reached a peak at 6 hr after the administration (Fig. 1). Further, GLAKAY was administered orally to six healthy young adults and six elderly persons at one capsule (15 mg of menatetrenone) three times daily after meals for 7 consecutive days. In the young adults, C_{max} and AUC after the final administration were approximately the same as those after the initial administration. In the elderly persons, on the other hand, C_{max} and AUC determined finally were about 1.3 times and about 1.5 times higher, respectively than those after the initial administration. The plasma concentration determined before the morning dose, stopped increasing on the third day.^{1, 2)}

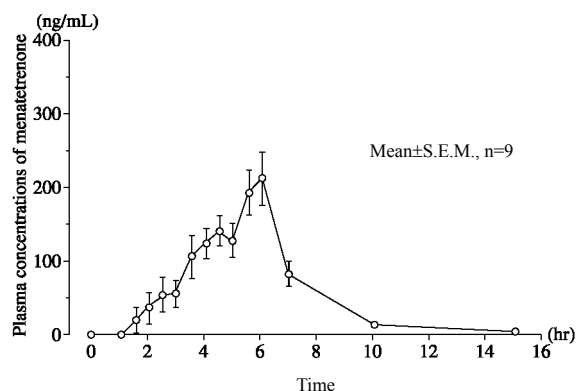


Fig. 1. Changes in mean plasma menatetrenone concentration after oral administration of one GLAKAY Capsules

Pharmacokinetic parameters of menatetrenone after oral administration of one GLAKAY Capsules

C_{max} (ng/mL)	t_{max} (hr)	AUC (ng · hr/mL)
253.2±82.4	4.72±1.52	870.7±149.6

(Mean±S.D., n=9)

2. Effect of meal

GLAKAY was administered orally to 3 healthy adult male volunteers at a dose of one capsule (15 mg of menatetrenone) after one night of fasting or within 30 min of breakfast, and the plasma menatetrenone concentration was determined. When GLAKAY was administered after one night of fasting, the absorption was found to be lower than that after breakfast (Fig. 2).³⁾

Eighteen healthy adult male volunteers were divided into 3 groups of 6 subjects each, and GLAKAY was administered orally to them at a dose of one capsule (15 mg of menatetrenone) within 30 mins of giving them a meal containing one of 3 different amounts of fat (fat content : 8.8 g, 20.0 g or 34.9 g) in accordance with a cross over design. When the plasma menatetrenone concentration was determined, it was found that the absorption of menatetrenone was greater according to the fat content of the meal. GLAKAY was administered orally to 12 of eighteen healthy adult male volunteers at a dose of one capsule (15 mg of menatetrenone) within 30 mins of giving them a meal containing a large amount of fat (53.8g). When the plasma menatetrenone concentration was determined, it was found that its absorption was similar to that for a meal with a fat content of 34.9 g (Fig. 3).⁴⁾

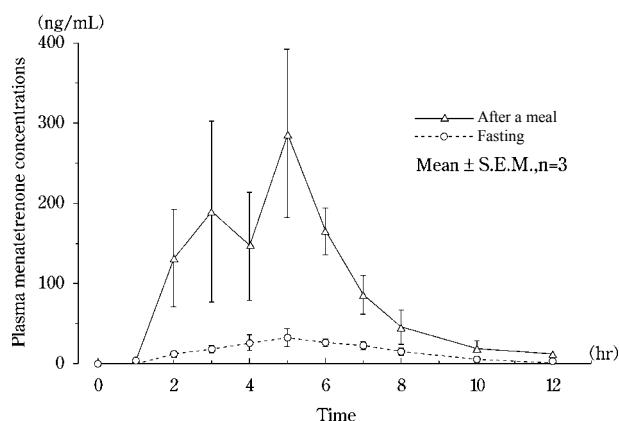


Fig. 2 Changes in mean plasma menatetretenone concentrations following administration of one GLAKAY Capsules in a fasting condition or after a meal

Pharmacokinetic parameters following oral administration of one GLAKAY Capsules during fasting or after a meal

Administration condition	C _{max} (ng/mL)	t _{max} (hr)	AUC (ng · hr/mL)
Fasting	32.3±18.2	4.3±1.2	165.00±73.54
After a meal	354.0±165.0	3.3±1.5	1,114.50±227.86

(Mean±S.D., n=3)

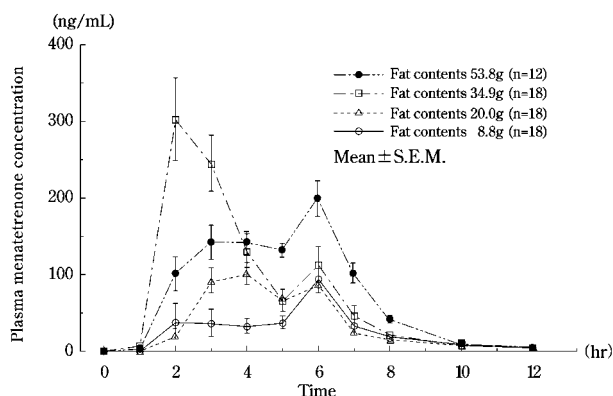


Fig. 3. Changes in mean plasma menatetretenone concentrations following oral administration of one GLAKAY Capsules after a meal containing one of 4 different amounts of fats

Pharmacokinetic parameters following oral administration of one GLAKAY capsule after a meal containing one of 4 different amounts of fats

Fat contents	C _{max} (ng/mL)	t _{max} (hr)	AUC (ng · hr/mL)
8.8g	133.4±80.5	5.3±1.5	370.6±194.2
20.0g	139.7±43.3	4.4±1.3	485.2±150.1
34.9g	409.4±159.1	3.0±1.5	1,024.4±341.4
53.8g	297.1±157.8	4.3±1.7	991.2±392.0

(Mean±S.D., n=18, case of 53.8g of fat contents, n=12)

Reference: Details of a meal containing 8.8 g of fat

Content	Quantity (g)	fat (g)
Rice	180	0.90
Miso soup	207	2.45
Boiled vegetables	170	0.18
Poached egg	84	5.10
Strawberry jelly	56	0.04
Banana (one piece)	100	0.10
Total	797	8.77

CLINICAL STUDIES

Clinical efficacy

1. Efficacy in patients with involuntional osteoporosis

In patients with postmenopausal or senile osteoporosis, the efficacy of GLAKAY was as follows: 51.9% (164/316 patients) were rated as “moderately to remarkably improved”; and 84.5% (267/316 patients) were rated as “fairly to remarkably improved”; and it was demonstrated that GLAKAY was effective in maintaining bone mass and reducing pain. The usefulness of GLAKAY was confirmed by a double blind clinical trial.^{5,6)}

In this trial (Phase III comparative study) pain was reduced when GLAKAY was administered alone in 57.2% (87/152 patients) and in 61.1% (66/108 patients) when it was co-administered with analgesics.

2. Efficacy in patients with secondary osteoporosis

The efficacy of GLAKAY in patients with secondary osteoporosis, including renal osteodystrophia, alcoholic osteopenia and steroidal osteopenia was as follows: 30.9% (17/55 patients) were rated as “moderately to remarkably improved”, and 60.0% (33/55 patients) were rated as “fairly to remarkably improved”.

PHARMACOLOGY

1. Improvement of experimental osteoporosis

- Both ovaries of 40-week old rats were resected and they were given low calcium feed for 3 months to produce a state of osteoporosis. Then, menatetretenone was administered orally to the rats at a dose of 30 or 100 mg/kg/day for 6 months. Menatetretenone inhibited reductions in femur splitting strength, bone calcium and hydroxyproline content. When menatetretenone was administered orally at a dose of 3 or 30 mg/kg/day for 6 consecutive months after ovariectomy, reductions in bone splitting strength, calcium and hydroxyproline content in the diaphysis were inhibited.⁷⁾
- Both ovaries of 13-week old rats were resected and menatetretenone was administered to them at a dose of 30 mg/kg/day for 8 weeks. Menatetretenone inhibited decrease in connectivity of three dimensional microarchitecture in trabecular bone.⁸⁾
- When adrenocortical hormone (10 mg/kg/day of prednisolone at 3 times a week) was administered intramuscularly to rats for 4 weeks, this resulted in reductions in bone splitting strength and bone calcium content. These reductions were inhibited after administering menatetretenone at a dose of 21 mg/kg/day for 4 consecutive weeks.⁹⁾

2. Mechanism of action

(1) Acceleration of osteogenesis

In human osteoblast cultures, calcification was accelerated by administration of menatetretenone at a concentration of 2.25×10^{-6} mol/L alone or when it was co-administered with $1,25(\text{OH})_2\text{D}_3$. The osteocalcin content in the cell layers was increased by coadministration with $1,25(\text{OH})_2\text{D}_3$.^{10,11)}

(2) Inhibition of bone resorption

In organ cultures of mouse calvaria, at concentrations of 3×10^{-6} to 3×10^{-5} mol/L, menatetrenone inhibited bone resorption induced by IL-1 α , PGE₂, PTH and 1,25(OH)₂D₃. In mouse bone marrow cell cultures, at concentrations of 3×10^{-6} to 1×10^{-5} mol/L, menatetrenone inhibited the induction of osteoclast release by 1,25(OH)₂D₃.^{12, 13)}

(3) Effect on serum level of osteocalcin

Menatetrenone was administered to patients with osteoporosis at a dose of 45 mg/day for 2 years. Menatetrenone increased the serum level of osteocalcin and decreased the serum level of Glu-osteocalcin.¹⁴⁾

REQUEST FOR LITERATURE SHOULD BE MADE TO:

Safety Management Department
Fax: 03-3811-2710
Eisai Co., Ltd.

REQUEST FOR DRUG INFORMATION SHOULD BE MADE TO:

Customer Information Service
Free Dial: 0120-419-497
Eisai Co., Ltd.

Manufactured and marketed by:

Eisai Co., Ltd.
6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo, 112-8088

PHYSICOCHEMISTRY

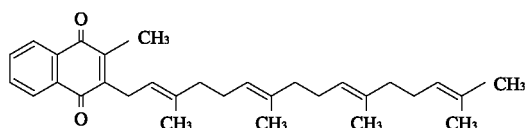
Nonproprietary name: Menatetrenone (JAN, INN)

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 material.

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 and the color becomes more intense by light.

Melting point: about 37°C

PACKAGING**GLAKAY Capsules 15 mg:**

Boxes of 100, 210 (21Caps. × 10), 1,000, 2,100 (21Caps. × 100) and 3,000 in press-through package, and bottles of 500

REFERENCES

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