Bon-One® 0.25 μgTablet
Bon-One®0.5 μgTablet
Bon-One® 1μg Tablet

< Alfacalcidol Preparations>

Storage
Store at temperature not exceeding 30°C in a dry place.

Expiration date
2 years from the date of production (The expiration date is specified on the outer package.)

DESCRIPTION

Brand name		Bon-One Tablet 0.25	Bon-One Tablet 0.5	Bon-One Tablet 1.0
Dosage form		Tablets		
Active ingredient	Name	Alfacalcidol		
	Content (per tablet)	0.25 μg	0.5 μg	1.0 μg
Inactive ingredient		Anhydrous lactose Povidone Propyl gallate Magnesium stearate		
Appearance	Face	TJN ONE	TJN ONE	TJN ONE
	Reverse	0.25	0.5	1.0
	Lateral			
	Size	Diameter 6.0mm Thickness 2.2mm		
Weight		85 mg	85 mg	85 mg
Identification code		TJN ONE: 0.25	TJN ONE: 0.5	TJN ONE: 1.0
Color/description		Odorless, white, circular uncoated tablets. The content of active ingredient is specified on the reverse.		

INDICATIONS
1.Improvement of various symptoms (hypocalcemia, tetany, bone pain, bone lesions, etc.) associated with abnormal vi-tamin D metabolism in the following diseases:
- Chronic renal failure
- Hypoparathyroidism
- Vitamin D-resistant rickets and osteomalacia

2.Osteoporosis

DOSAGE AND ADMINISTRATION
The dosage of Bon-One Tablet should be adjusted according to careful monitoring of the patient's serum calcium level.
1. Chronic renal failure and osteoporosis:
The usual adult oral dosage of Bon -One Tablet is 0.5-1.0 μg of alfacalcidol, once daily. The dosage should be adjusted according to the patient's age and symptoms as deemed appropriate.
2. Hypoparathyroidism, and other diseases associated with abnormalities of vitamin D metabolism:
The usual adult oral dosage of Bon-One Tablet is 1.0-4.0 μg of alfacalcidol, once daily. The dosage should be adjusted according to the disease, age, symptoms, and disease type, as deemed appropriate.
(Pediatric dosage)
The usual oral dosage of Bon-One Tablet for osteoporosis in children is 0.01-0.03 μg/kg of alfacalcidol once daily, and for other diseases 0.05-0.1 μg/kg of alfacalcidol once daily. The dosage should be adjusted according to the disease and symptoms.

PRECAUTIONS
1.Important Precautions
1) In order to avoid overdosage, serum calcium levels should be determined periodically during administration, and the dosage should be adjusted so that the serum calcium level does not exceed the normal range.
2) If hypercalcemia develops, Bon-One Tablet should be immediately discontinued. If the serum calcium level returns to the normal range after the discontinuation, restart Bon-One Tablet administration at a lower dose.

2. Drug Interactions
Precautions for coadministration (Bon-One Tablet should be administered with care when coadministered with the following drugs.)

Drugs	Signs , Symptoms and Treatment	Mechanism and Risk Factors
Preparations containing magnesium (e.g., magnesium oxide, magnesium carbonate)	Occurrence of hypermagnesemia has been reported.	Unknown
Digitalis preparations (e.g., di-goxin)	Arrhythmia may occur.	The effects of digitalis preparations will be enhanced if hypercalcemia develops as a result of taking Bon-One Tablet.
Calcium preparations (e.g., calcium lactate hydrate, calcium carbonate)	Hypercalcemia may occur.	Bon-One Tablet promotes the intestinal absorption of calcium.
Vitamin D and its derivatives (e.g., calcitriol)	Hypercalcemia may occur.	Additive effect
PTH preparation (teriparatide)	Hypercalcemia may occur.	Additive effect

3. Adverse Reactions
The incidence of adverse reactions in Japan at the time of approval and in the Drug-use results surveys is described below. (Data collected at the completion of the Reexamination).
1) Improvement of symptoms and signs associated with abnormalities of vitamin D metabolism in chronic renal failure, hypoparathyroidism, vitamin D-resistant rickets and osteomalacia, and premature infants.
A total of 471 adverse reactions were observed in 285 (5.7%) of 4,967 patients evaluated. The major adverse reactions were 112 events of itching (2.3%), 48 events of anorexia (1.0%), 47 events of feeling queasy(0.9%), 28 events of diarrhoea (0.6%), 27 events of ALT (GPT) increased (0.5%), etc.
2) Osteoporosis
A total of 241 adverse reactions were observed in 192 (1.3%) of 14,808 patients evaluated. The major adverse reactions were 24 events of BUN increased (0.2%), 23 events of feeling queasy (0.2%), 21 events of anorexia (0.1%), 19 events of stomachache (0.1%), 14 events of AST (GOT) increased (0.09%), etc.

(1) Clinically Significant Adverse Reactions
1) Renal failure acute (Incidence unknown): Renal failure acute with serum calcium increased may occur. Serum calcium level and renal function should be periodically monitored, and if any abnormality is observed, appropriate measures, such as discontinuing administration, should be taken.
2) Hepatic function disorder, jaundice (Incidence unknown): Hepatic function disorder and/or jaundice, with AST (GOT) increased, ALT (GPT) increased, ALP increased, etc., may occur. The patient should therefore be carefully monitored. If any abnormal findings are observed, administration should be discontinued and appropriate measures should be taken.

(2) Other Adverse Reactions
If the following adverse reactions are observed, appropriate measures, such as dose reduction or discontinuation of administration, should be taken.

Incidence /Organ system	5%> ≥0.1%	<0.1%
Gastrointestinal	Anorexia, Nausea/ Feeling queasy, Diarrhoea, Constipation, Stomachache	Vomiting, Abdomen enlarged feeling, Stomach discomfort, Dyspepsia, Oral cavity discomfort, Thirst, etc.
Psychoneurologic		Headache/Headache dull, Sleep loss/Feeling irritated, Weakness/Malaise, Dizziness, Numbness, Sleepiness, Hypomnesia, Tinnitus, Presbycusis, Back pain, Shoulder muscle stiffness, Cramps of lower extremities, Chest pain, etc.
Cardiovascular		Mild blood pressure increased, Palpitation
Hepatic	AST (GOT) increased, ALT (GPT) increased	LDH increased, γ-GTP increased
Renal	BUN increased / Creatinine increased (Renal function de-creased)	Calculus renal
Dermatologic	Itching	Rash, Skin warm
Ophthalmic	Conjunctival hyperaemia	
Skeletal		Peri-articular calcifi-cation (Excessive bone formation)
Other		Hoarseness, Oedema

4. Use in the Elderly
Since physiological function is generally decreased in the elderly, caution should be exercised in the dosage.

5.Use during Pregnancy, Delivery or Lactation
(1) Bon-One Tablet should be administered to pregnant or possibly pregnant women only when the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this Product in pregnancy has not been established. In animal experiments (in rats) at large doses, delayed fetal ossification and effects on the gonads were observed, and a decrease in pregnancy rate, increase in fetal mortality rate, fetal development suppression, decreased nursing ability, etc. were observed.[1-3)]]
(2) It is advisable to avoid using Bon-One Tablet in lactating women. If the administration is judged to be essential, breast-feeding must be discontinued during the administrationt. [The safety of this Product in lactating women has not been established. In animal experiments (in rats), drug transfer rate to suckling newborns corresponds to 1/20 of the dose administered to the moth-er.[4)]]

6. Pediatric Use
When used in children, Bon-One Tablet should be administered cautiously to avoid overdosage: e.g. administration should be started at a low dosage and gradually increased while monitoring serum calcium levels and the urinary calcium/creatinine ratio. [More intense oral acute toxicity was observed in juvenile rats than in adult rats.5)]

7. Precautions Concerning Use
Precautions regarding dispensing: 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, resulting in serious complications such as mediastinitis.]

8. Other Precautions
When used in patients with hyperphosphatemia, reduce serum phosphorus level by coadministering phosphorus-binding agent.

PHARMACOKINETICS
Alfacalcidol is absorbed in the small intestine, and converted to 1α,25-$(OH)_2D_3$ in the liver.[6)] When Bon-One Tablet 4.0 μg (1.0 μg x 4 tablets) was orally administered to 14 healthy adults, the blood 1α,25-$(OH)_2D$ concentration reached the maximum (mean: 94.6 pg/mL) at 4-24 hours after the administration (mean: 11.0 hours) and almost returned to the pre-dosing level at 48-72 hours.[7)]

(Reference Information)
Absorption and Excretion
When 0.4 μg/kg of alfacalcidol was orally administered to rats, approximately 72% was excreted in the urine and feces within 48 hours, and almost 100% was excreted by 7 days.[8)]
When alfacalcidol was administered to rats for 14 consecutive days, no tendency to accumulate in the major organs was observed.[9)]

CLINICAL STUDIES
Clinical Efficacy
The efficacy rates in open clinical studies conducted in 22 institutions in Japan (totally 30 institutions) are shown below.[10-14)]

Diseases \ Efficacy rate (%)	Effective or better
Chronic renal failure	70.9% (90/127)
Osteoporosis	51.4% (95/185)

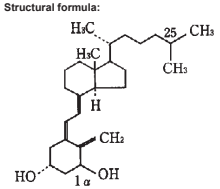
Efficacy was also observed in double-blind clinical studies for osteoporosis and chronic renal failure conducted with Onealfa* Capsule.[15),16)] Biological equivalence of Bon-One Tablet and Onealfa* Capsule was confirmed.
*"*Onealfa" is the trademark of Teijin Pharma Limited in Japan corresponding to "Bon-One".*

PHARMACOLOGY
After oral administration, alfacalcidol is rapidly absorbed into the blood from the intestine, and the side chain at position 25 is hydrolyzed by 25-hydroxylase of hepatic microsomes to form active substance 1α,25-$(OH)_2D_3$. The active substance binds to receptors distributed in the target tissues, such as the intestine and bone, where it expresses a series of physiological activities, including promoting calcium absorption from the intestine, bone mineral dissolution, osteogenic activities, etc.
1. Effects to promote intestinal calcium absorption and increase serum calcium level
Effects to promote intestinal calcium absorption and increase serum calcium level were observed in animal experiments in which alfacalcidol was given to vitamin D-deficient rats and nephrectomized rats.[17),18)]

2. Osteogenesis-promoting effects
1) Bone tissue culture
A study in cultures of embryo tissue collected from 9-day chick eggs has demonstrated that 1α,25-$(OH)_2D_3$ is essential for normal osteogenesis.[19)]
2) Nephrectomized rats
Bone neogenesis was observed in animal experiments in which alfacalcidol was administered for 30 days to rats that received subtotal nephrectomy and developed a large number of bone resorption spaces, and significant increase of osteoid layer and hypocalcification layer.[20)]
3) Osteoporosis model rats (ovariectomized rats)
Decreases in serum 1α,25-$(OH)_2D_3$ level, trabecular bone, and mineralization rate occur after long-term raising of ovariectomized rats. These changes were corrected when alfacalcidol, 0.1 μg/kg/day, was admi-nistered for 6 months.[21)]
4) Osteoporosis model rats (hydrocortisone-treated rats)
Decreases in trabecular bone, cortical width, and bone composition occur as a result of long-term hydrocortisone administration to rats. These changes were corrected when alfacalcidol, 0.02 μg/kg/day - 0.1 μg/kg/day, was administered for 12 weeks.[22)]
5) Senile osteoporosis (humans, electron microscopic and light microscopic observations)
Iliac bones were biopsied before and after administration of Onealfa* Capsule, and examined by light and electron microscopes. Improvements in the bone histological characteristics were observed, e.g., increases in active osteoblasts, osteocytes, and mineralized bone scrobiculus.[23)]
* "Onealfa" is the trademark of Teijin Pharma Li-mited in Japan corresponding to "Bon-One".
6) Amount of calcium intake and effects on bone re-sorption/formation
In animal experiments in which alfacalcidol was given to vitamin D-deficient rats that were fed different contents of calcium in their diet, bone resorption was observed under low calcium contents, but bone formation was markedly observed under sufficient calcium contents.[17)]

PHYSICOCHEMISTRY
Nonproprietary name: Alfacalcidol
Chemical name:
(5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-1α,3ß-diol

Structural formula:



Molecular formula: $C_{27}H_{44}O_2$
Molecular weight: 400.64
Melting point: 137-142°C
Description:
Alfacalcidol occurs as white crystal or crystalline powder. It is freely soluble in methanol, in ethanol (99.5), in chloroform, and in dichloromethane, soluble in acetone and in diethyl ether, and practically insoluble in water and in hexane.

Storage
Store at temperature not exceeding 30°C, in dry place.

PACKAGING:
Carton box containing 3 (Al/ transparent (PVC/PVDC) strips, each containing 10 tablets each strips kept in aluminium foil sealed bag with a desiccant + insert leaflet.

Expiration date
2 years from the date of production (the expiration date is specified on the outer package).

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