Active Form of Vitamin D3

No. of Standard Commodity Classification for Japan: 873112

Powerful Bon-One® Tablet (0.25, 0.5, 1.0μg)

Alfacalcidol

Approval No.: 0.25μg; (62AM)No. 871, 0.5μg; (62AM)No.872, 1.0μg; (62AM)No.873

Bon-One® tablet was developed by Teijin Ltd., Japan, and is an agent for the improvement of Ca metabolism and for the promotion of bone formation. Bon-One® becomes active form after being metabolized into 1α, 25-$(OH)_2$-D_3 by 25-hydroxylase in liver and it acts on intestine, kidney, parathyroid glands, and bone tissue to normalize serum Ca level, and improves various types of bone lesions. Bon-One® tablet is clinically confirmed to be useful in osteoporosis, chronic renal failure, hypoparathyoidism and osteomalasia.

<Composition>

Each Bon-One® tablet contains 0.25, 0.5 or 1.0 μg of alfacalcidol.

<Indications>

- Improvement of various symptoms (hypocalcemia, tetany, bone pain, bone lesions, etc.) due to abnormal vitamin D metabolism in the following conditions:
  - •Chronic renal failure
  - •Hypoparathyroidism
  - •Vitamin D-resistant rickets and osteomalacia
- Osteoporosis

<Dosage and Administration>

The dose should be adjusted with careful monitoring of the serum Ca level.

- Chronic renal failure and osteoporosis:
  For adults, 0.5 ~ 1.0 μg, as alfacalcidol, of Bon-One® tablet is generally administered orally once a day. The dose should be adjusted according to the age of the patients and the severity of symptoms.
- Hypoparathyroidism and other diseases associated with abnormal vitamin D metabolism:
  For adults, 1.0 ~ 4.0 μg, as alfacalcidol, of Bon-One® tablet is generally administered orally once a day. The dose should be adjusted according to the dieases, age of the patients, severity of symptoms, and the type of the diseases.

Dosage for children:
The general oral dose for children with osteoporosis ranges 0.01 ~ 0.03 μg/kg as alfacalcidol once a day, and that for the other indications ranges 0.05 ~ 0.1μg/kg as alfacalcidol once a day. The dose should be adjusted according to the diseases and the symptoms.

<Precautions>

1. General precautions
   (1) To avoid overdose, the dose should be adjusted to keep the serum Ca level within normal range by the periodical monitoring.
   (2) In case of hypercalcemia, treatment with Bon-One® tablet should be stopped immediately. After the serum Ca level returns to normal, the treatment shall be reinitiated at a lower dose.
2. Drug interactions
   Careful attention should be paid to concomitant use.
   (1) Magnesium-containing preparations (Hypermagnesemia is reported to occur)
   (2) Digitalis preparations (In case hypercalcemia is caused by Bon-One® tablet, the activity of digitalis preparation may be increased to cause arrhythmia.)
3. Adverse reactions (rarely: <0.1%, infrequently: 0.1 ~ <5%, no specific designation:≧5% or frequency unknown)
   1) Gastrointestinal:
   Anorexia, nausea/vomiting, abdominal distention, diarrhea, constipation, stomach pain, and/or stomach discomfort may infrequently occur. Dyspepsia, oral cavity discomfort and thirst may rarely occur.
   2) Psychoneurologic:
   Headache/dull headache, insomnia/feeling irritated, weakness, malaise, dizziness, feeling of numbness, sleepiness, failure of memory, tinnitus, presbycusis, back pain, shoulder stiffness, feeling of spasticity of the lower limbs, and/or chest pain may rarely occur.
   3) Cardiovascular:
   Slight increase of blood pressure and/or palpitation may rarely occur.
   4) Hepatic:
   Elevation of GOT, GPT, LDH, and/or γ-GTP may infrequently occur.
   5) Renal:
   Elevation of BUN and/or sCr (indicating decreased renal function) and renal calculus may rarely occur.
   6) Dermatologic:
   Itching and/or rash may infrequently occur. Hot feeling may rarely occur.
   7) Ophthalmic:
   Conjunctival congestion may infrequently occur.
   8) Osseous:
   Ectopical calcification (calculus) around joints may rarely occur.
   9) Others:
   Edema and/or hoarseness may rarely occur.
4. Use in the elderly
   Attention to the dose should be required due to generally lower physiologic functions.
5. Use during pregnancy
   Delayed ossification was observed in fetal rats at high doses. Since the safety of Bon-One® tablet during pregnancy has not been established, administration to pregnant women or women suspected in pregnancy should be limited to the cases where the therapeutic benefit is judged to outweigh the potential risks.
6. Pediatric use
   Acute toxicity in young rats is more remarkable than in matured rats. For administration to children, Bon-One® tablet should be carefully used to avoid overdose ex., by gradual dose increase after initial lower dose under close monitoring of serum Ca level, urinary Ca level, and urinary Ca/Cr. ratio.
7. Overdosage
   Many cases of adverse reactions are considered to be caused by hypercalcemia. Therefore, in case of adverse reactions, monitoring of serum Ca level is appropriate. Refer to General Precautions for the treatment.
8. Cautions in use (For doctors and/or pharmacists)
   Instruction for patients to administer the tablet only, after putting it out of the blister pack, shall be required.
9. Others
   In case of administration to patients with hyperphosphatemia, the serum phosphate level should be reduced using phosphate binders.

<Pharmacology>

Following oral administration, Bon-One® tablet is rapidly absorbed into blood through intestine and the 25-position of the side-chain is hydroxylated, with 25-hydroxylase of hepatic microsome, into the final active substance, 1α, 25-$(OH)_2D_3$. It binds with receptors in intestinal tract, bone and the other target organs, and develops series of physiological activities, such as promotion of Ca absorption from intestine, bone resorption, and bone formation activities.

1. Promotion of Ca absorption from intestine and elevation of serum Ca [1) 2)]
   Promotion of Ca absorption from intestine and elevation of serum Ca level were observed in experiment with vitamin D deficient rats and nephrectomized rats.
2. Promotion of bone formation
   (1) Bone tissue culture [18)]:
   A culture study with tissue collected from 9-day old chicken fetus proved essentiality of 1α, 25-$(OH)_2D_3$ for formation of normal bone.
   (2) Nephrectomized rats [3)]:
   Bone neogenesis was observed, after 30 days administration of alfacalcidol, in rats with many multiple bone absorption cavities, osteoid layer, and remarkably increased hypocalcification layer caused by subnephrectomy.
   (3) Osteoporosis model rats (ovariectomized rats [19)]):
   Long-term fed ovariectomized rats decreased serum 1α, 25-$(OH)_2D_3$ level and reduced cancellous bone as well as Ca deposit rate. All of the deterioration above were improved by administration of alfacalcidol 0.1 μg/kg/day for six months.
   (4) Osteoporosis model rats (hydrocortisone-treated rats [20)]):
   Long-term administration of hydrocortisone developed reduction in cancellous bone mass, bone cortex width and bone components. These changes were improved by administration of alfacalcidol 0.02 ~ 0.1 μg/kg/day for 12 weeks.
   (5) Senile osteoporosis (electron/light microscopic observations, human [21)]):
   Before and after administrations of Bon-One® capsule, the specimens collected by iliac biopsy was observed by electron/light microscopies. Osteohistological improvements, such as increase in active osteoblast, osteocyte and calcificated bone scrobiculus, were observed.
   (6) Intake amount of Ca and the effect on bone resorption/bone formation[1)]:
   In vitamin D deficient rats, fed with variety amounts of Ca diet, under administration of alfacalcidol, bone resorption was observed in lower Ca group and not in sufficient Ca group.

<Pharmacokinetics>

Bon-One® is absorbed at small intestine, and rapidly metabolized into 1α, 25-$(OH)_2$-D_3 in liver [15]. The peak serum level is observed at 8 ~ 24 hours after the administration and the half life is 2 ~ 4 days in normal adults with oral administration of Bon-One® capsule 4 μg /day [16].

<Clinical application>

1. Clinical effect

Effect of Bon-One® tablet in clinical trials at 22 institutions (30 in total) is as follows.

(1) Chronic renal failure, etc. [23] [25] [26]

In 127 cases, 70.9% (90/127) was effective or very effective, and 87.4% (111/127) moderately effective or better.

(2) Osteoporosis [24] [25] [26]

In 185 cases, 51.4% (95/185) was effective or very effective, and 85.9% (159/185) moderately effective or better.

2. Adverse reactions including changes in laboratory data

Safety of Bon-One® tablet in 333 cases of clinical trials at 22 institutions (30 in total) is as follows.

* Chronic renal failure, etc. [23] [25] [26]

No adverse reaction was noted in 142 cases. No definite change in laboratory data was observed.

* Osteoporosis [24] [25] [26]

In 191 cases, only 1 case of eczema (0.5%) was observed. It disappeared after stopping the administration. No definite variation in laboratory data was observed.

Safety of Bon-One® capsule, which has an identical bioequivalence in ADME patterns to Bon-One® tablet, in 9,802 cases at 1,356 institutions (including the data in NDA and 6-year-long PMS) is as follows.

* Chronic renal failure

(a) In 707 cases in NDA, 66 cases of adverse reactions (9.34%) were observed. The most common ones were itching in 33 cases (4.67%), anorexia in 10 cases (1.41%), nausea/vomiting in 10 cases (1.41%), etc.

(b) In 1,207 cases in 6-year-long PMS (Oct. '80 ~ Oct. '86), 62 cases of adverse reactions (5.14%) included itching in 20 cases (1.66%) nausea/vomiting in 10 cases (0.83%), elevation of GPT in 8 cases (0.66%), etc.

* Osteoporosis

(a) In 483 cases in NDA, 20 cases of adverse reactions (4.14%) were observed. The most common ones were anorexia in 5 cases (1.04%), nausea, vomiting in 4 cases (0.83%), etc.

(b) In 7,405 cases in 3-year-long PMS (Oct. '83 ~ Oct. '86), 100 cases of adverse reactions (1.35%) were observed. The most common ones were elevation of BUN/Cr. in 22 cases (0.30%), GOT in 13 cases (0.18%), GPT in 11 cases (0.15%), γ-GTP in 8 cases (0.11%), stomach disconformt in 7 cases (0.09%), etc.

<Pre-clinical studies>

1. Acute toxicity (LD_{50} μg/kg) [1] [6]

Animal / Route / Sex	Mice ♂	Mice ♀	Rats ♂	Rats ♀	Dogs ♂	Dogs ♀
Oral Administration	476	440	340	720	500-700	500-700

2. Subacute and chronic toxicity

In Wistar rats given alfacalcidol 50μg/kg or less for 1 month orally [4], 5.0 μg/kg or less for 3 months [5] and 2.5 μg/kg or less for 6 months [7], and in beagle dogs given 10 μg/kg or less for 1 month orally [9] and 0.08μg/kg or less for 12 months [8], no remarkable abnormality was observed in rats given 2.5μg/kg for 1 month and 0.1μg/kg for 3 ~ 6 months, and in beagle dogs given 0.04μg/kg for 1 month and 0.02 μg/kg for 12 months. In high dose groups, secondary changes due to overdose of alfacalcidol were observed, i.e., atrophies of the thymus and gonad, and degeneration of myocardium and renal tubules. These findings were recovered following discontinuation of the administration.

3. Reproduction studies

2.5 μg/kg or less was orally administered to rats, before and in the early stage of pregnancy [6], organogenetic period [10], and perinatal and nursing periods [12], and 0.5μg/kg or less to rabbits in organogenesis stage [11] respectively. No remarkable abnormality was observed in rats at 0.5 μg/kg and rabbits at 0.02 μg/kg. In high dose groups, delayed ossification, influences to the gonad, reduction of fertility, increased fetal death rates, inhibition of fetal development, and reduction in nursing activity were noted.

4. Specific toxicity

No abnormality was observed in antigenicity and mutagenicity tests [13].

5. Absorption/Excretion in rats

Rats orally given 0.4 μg/kg excreted 72% of the dose into the urine and stool within 48 hours and almost 100% within 7 days [14]. Rats given alfacalcidol for 14 consecutive days showed no accumulation in the major organs [17].

<Description>

1. Description of the preparation

Bon-One® tablet is a white, round uncoated tablet. It has no odor. The content of the active ingredient is indicated on the tablet.

	Appearance		
	Top	Bottom	Side
0.25μg	TJN ONE	0.25	6.0mm / 2.2mm
0.5 μg	TJN ONE	0.5	6.0mm / 2.2mm
1.0 μg	TJN ONE	1.0	6.0mm / 2.2mm

2. Physiochemical properties of the active ingredient

Generic name : Alfacalcidol

Chemical name : 9, 10-secocholesta-5, 7, 10 (19)-triene 1α, 3β-diol

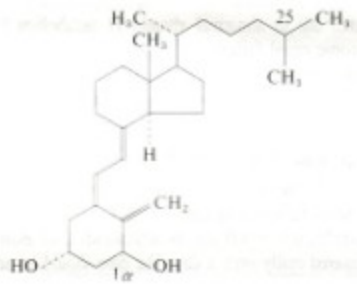
Molecular formula : $C_{27}H_{44}O_2$

Molecular weight : 400.64

Melting point : 137 ~ 142℃

Description : Alfacalcidol is white crystal or crystalline powder, and is freely soluble in methanol, dehydrate ethanol, chloroform or dichloromethan, soluble in acetone or diethyl ether, and practically insoluble in water or hexane.

Chemical structure:



<Handling Precautions>

1. Regulatory Classification: Powerful drug.
2. Storage : Store at room temperature shielded from humidity and light.
3. Shelf life : 3 years. Refer to the expiry date on the package.

<Package>

Blister package

0.25, 0.5, 1.0 μg : 100 tablets (10 tablets × 10)

Bottled package

0.25, 0.5, 1.0 μg : 500 tablets

<References>

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