TOWA PHARMACEUTICAL CO., LTD.

**Revised: July 2015 (_____part: 13th version, Section of Description)
*Revised: December 2013 (_____part)

ACTIVATED VITAMIN-D_3 PREPARATION

Powerful drug

*ALFACALCIDOL CAPSULES 0.25μg "TOWA"
*ALFACALCIDOL CAPSULES 0.5μg "TOWA"
*ALFACALCIDOL CAPSULES 1μg "TOWA"

(Alfacalcidol Capsules)

Storage:
Protect from light and store at room temperature.
Expiration date:
Indicated on the package and label.

Standard Commodity Classification No. of Japan 873112			
	Approval No.	Date of listing in the NHI reimbursement price	Date of initial marketing in Japan
Capsule 0.25μg	22500AMX01143	December 2013	July 1992
Capsule 0.5μg	22500AMX01092	December 2013	July 1992
Capsule 1μg	22500AMX01099	December 2013	July 1992

COMPOSITON AND PRODUCT DESCRIPTION

Product name	ALFACALCIDOL CAPSULES 0.25μg "TOWA"	ALFACALCIDOL CAPSULES 0.5μg "TOWA"	ALFACALCIDOL CAPSULES 1μg "TOWA"
Active ingredient per capsule	Alfacalcidol ·····0.25 μg	Alfacalcidol ····· 0.5 μg	Alfacalcidol ·····1.0 μg
Inactive ingredients	Anhydrous Ethanol, Medium Chain Fatty Acid Triglyceride Capsule: Gelatin, Concentrated Glycerin, D-Sorbitol Solution, Titanium Oxide, Yellow Ferric Oxide	Anhydrous Ethanol, Medium Chain Fatty Acid Triglyceride Capsule: Gelatin, Concentrated Glycerin, D-Sorbitol Solution, Titanium Oxide	Anhydrous Ethanol, Medium Chain Fatty Acid Triglyceride Capsule: Gelatin, Concentrated Glycerin, D-Sorbitol Solution, Titanium Oxide, Red Ferric Oxide
Product description	Pale yellow to light yellow soft capsule Content: Colorless to pale yellow clear, liquid with a faint, characteristic odor.	White to pale yellowish white soft capsule Content: Colorless to pale yellow clear, liquid with a faint, characteristic odor.	Pale red to light red soft capsule Content: Colorless to pale yellow clear, liquid with a faint, characteristic odor.
Identification mark	Package: Tw.$D_3$0.25	Tw.$D_3$0.5	Tw.$D_3$1.0
Appearance Length	Side surface:  About 9.0mm	 About 9.0mm	 About 9.1mm
	Cross section:  About 5.9mm	 About 5.9mm	 About 6.2mm
Weight (mg)	About 185	About 185	About 205

INDICATIONS

○ Osteoporosis
○ Improvement of symptoms resulting from disorders of vitamin D metabolism (hypocalcemia, tetany, bone pain, osseous lesions, etc.) in the following diseases:
Chronic renal failure, hypoparathyroidism, vitamin-D-resistant rickets, and osteomalacia.

DOSAGE AND ADMINISTRATION

The dosage of this product should be adjusted with careful monitoring of the serum calcium level.

○ Osteoporosis and chronic renal failure
The usual adult dosage for oral use is 0.5-1.0 μg of alfacalcidol once daily.
The dosage may be adjusted according to the patient's age and symptoms.
○ Hypoparathyroidism and other diseases resulting from disorders of vitamin D metabolism.
The usual adult dosage for oral use is 1.0-4.0 μg of alfacalcidol once daily.
The dosage may be adjusted according to the kinds and types of diseases and patient's age and symptoms.

[Pediatric dosage]
The usual pediatric dosage for oral use is 0.01-0.03 μg/kg of alfacalcidol once daily for the treatment of osteoporosis and is 0.05-0.1 μg/kg of alfacalcidol once daily for other diseases.
The dosage may be adjusted according to the diseases and patient's symptoms.

PRECAUTIONS

1. Important Precautions

1) In order to prevent overdosage, the serum calcium level should be measured periodically while the patient is receiving this product. The dosage should be adjusted to ensure that the serum calcium level is maintained within the normal range.
2) If **hypercalcemia** occurs, administration of this product should be suspended immediately. Treatment may be resumed at a reduced dosage once the serum calcium level has reached the normal range after cessation of the drug.

2. Interactions

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

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Magnesium-containing drugs: Magnesium oxide, Magnesium carbonate, etc.	Hypermagnesemia has been reported.	The mechanism is not known.
Digitalis preparations: Digoxin, etc.	Arrhythmia may occur.	When hypercalcemia is induced by the administration of this product, the effects of digitalis are enhanced.

Calcium preparations: Calcium lactate hydrate, Calcium carbonate, etc.	Hypercalcemia may occur.	This product accelerates the absorption of calcium in the intestinal tract.
Vitamin D and its derivatives: Calcitriol, etc.	Hypercalcemia may occur.	This is due to the additive effect of this product.
PTH preparation Teriparatide	Hypercalcemia may occur.	This is due to the additive effect of this product.

3. Adverse Reactions

No investigation such as a post-marketing surveillance clearly showing the incidence of adverse reactions has been conducted.

1) **Clinically significant adverse reactions** (incidence unknown)

(1) **Acute renal failure**: Acute renal failure associated with increased serum calcium may occur. Patients should be carefully monitored periodically for serum calcium levels and renal function. If any abnormal findings are observed, appropriate measures such as discontinuing administration should be taken.

(2) **Hepatic dysfunction and jaundice**: Hepatic dysfunction and jaundice associated with increased AST (GOT), ALT (GPT), or Al-P may occur. Patients should be closely monitored during the course of administration. If any abnormal findings are observed, administration of this product should be discontinued and appropriate measures taken.

2) **Other adverse reactions**

If any of the following adverse reactions are observed, appropriate measures such as dosage reduction or discontinuation of treatment should be taken.

	Incidence unknown
Gastrointestinal	Anorexia, nausea and vomiting, diarrhea, constipation, stomachache, vomiting, abdominal fullness, stomach discomfort, dyspepsia, oral discomfort, thirst, etc.
Psychoneurologic	Headache/dull headache, insomnia/irritated feeling, weakness /malaise, dizziness, numbness, sleepiness, diminished memory/ registration capacity, tinnitus, presbycusis, back pain, shoulder stiffness, cramped feeling in the legs, chest pain, etc.
Cardiovascular	Mildly elevated blood pressure, palpitations
Hepatic	Increased AST (GOT), increased ALT (GPT), increased LDH, increased γ-GTP
Renal	Increased BUN, increased creatinine (reduced renal function) renal calculus
Dermatologic	Itching, rash, feeling of heat
Ophthalmic	Conjunctival congestion
Osseous	Periarticular calcification (ossification)
Others	Hoarseness, edema

4. Use in the Elderly

Since the physiological function is generally reduced in elderly patients, the dosage should be adjusted with care.

5. Use during Pregnancy, Delivery, or Lactation

1) This product should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product in pregnant women has not been established. Animal studies (in rats) have shown that administration of this product in large doses results in delayed development such as delayed ossification in fetuses.]

2) Administration of this product to lactating mothers is not recommended. If use of this product is judged to be essential, breast feeding must be discontinued during treatment. [The safety of this product in lactating mothers has not been established. In animal studies (in rats), transfer rate of this product to newborn offspring through milk is equivalent to one twentieth of the administered dose to lactating rats.]

6. Pediatric Use

Caution should be exercised to avoid overdose and appropriate measures, such as increasing the dose gradually from a low level with close monitoring of serum calcium levels, be taken when this product is administered to children. [An animal study has shown that the oral acute toxicity was greater in young rats than in adult rats.]

7. Precautions Concerning Use

Precautions regarding dispensing:

For drugs that are dispensed in a PTP (press-through package) sheet, 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 severe complications such as mediastinitis.]

8. Other Precautions

When this product is administered to patients with hyperphosphatemia, a phosphate-binding agent should be coadministered to reduce serum phosphate levels.

PHARMACOKINETICS

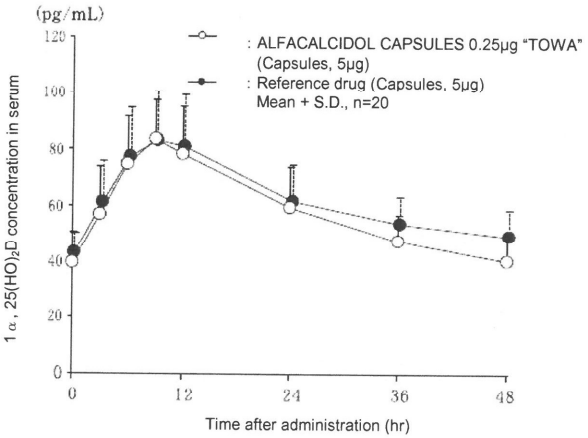
Bioequivalence test

1) ALFACALCIDOL CAPSULES 0.25μg "TOWA"

Twenty capsules each of ALFACALCIDOL CAPSULES 0.25μg "TOWA" and a reference drug (as 5 μg of alfacalcidol) were administered orally as a single dose to healthy adult men (n=20) under fasting conditions in a crossover design to measure each 1α, $25(OH)_2D$* concentration in serum. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed. The analysis results confirmed the bioequivalence of these drugs. (based on PAB/PCD Notification No. 718, May 30, 1980)[1].

(Note) A single oral dose of 5 μg is unapproved.

*1α, $25(OH)_2D$: Active metabolite, 1α, $25(OH)_2D_3$ of Alfacalcidol + Biological origin, 1α, $25(OH)_2D_2$



	Determined parameter		Reference parameter
	AUC_{48} (pg·hr/mL)	Cmax (pg/mL)	Tmax (hr)
ALFACALCIDOL CAPSULES 0.25μg "TOWA" (Capsules, 5μg)	2805.6±515.1	86.5±14.2	10.2±3.9
Reference drug (Capsules, 5μg)	3005.6±550.9	86.6±18.7	8.9±2.7

(Mean ± S.D., n=20)

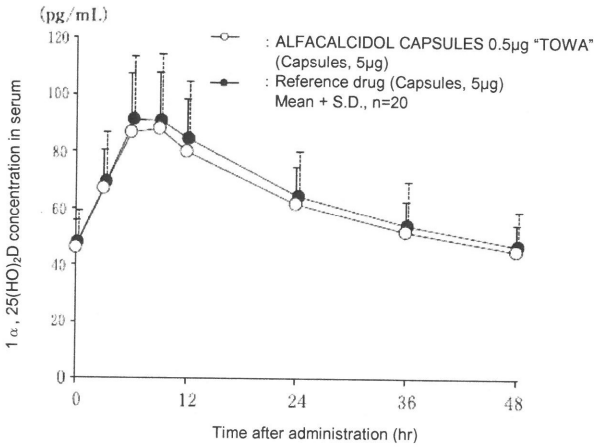
Serum concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

2) ALFACALCIDOL CAPSULES 0.5μg "TOWA"

Ten capsules each of ALFACALCIDOL CAPSULES 0.5μg "TOWA" and a reference drug (as 5 μg of alfacalcidol) were administered orally as a single dose to healthy adult men (n=20) under fasting conditions in a crossover design to measure each 1α, $25(OH)_2D$* concentration in serum. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed. The analysis results confirmed the bioequivalence of these drugs. (based on PAB/PCD Notification No. 718, May 30, 1980)[1].

(Note) A single oral dose of 5 μg is unapproved.

*1α, $25(OH)_2D$: Active metabolite, 1α, $25(OH)_2D_3$ of Alfacalcidol + Biological origin, 1α, $25(OH)_2D_2$



	Determined parameter		Reference parameter
	AUC_{48} (pg·hr/mL)	Cmax (pg/mL)	Tmax (hr)
ALFACALCIDOL CAPSULES 0.5μg "TOWA" (Capsules, 5μg)	3017.5±577.7	91.6±21.2	8.6±2.0
Reference drug (Capsules, 5μg)	3160.8±735.9	96.4±25.0	7.7±1.8

(Mean ± S.D., n=20)

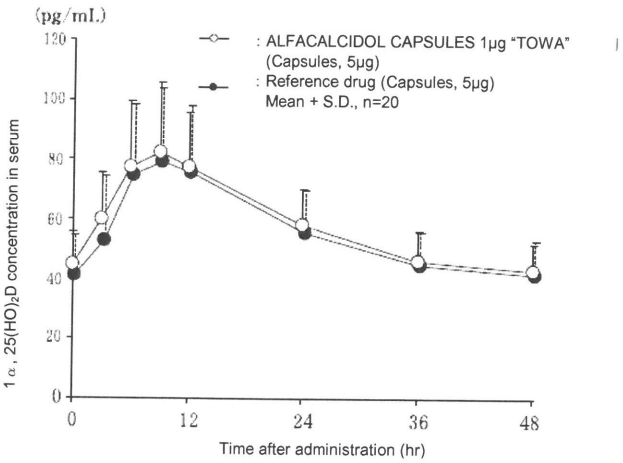
Serum concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

3) ALFACALCIDOL CAPSULES 1μg "TOWA"

Five capsules each of ALFACALCIDOL CAPSULES 1μg "TOWA" and a reference drug (as 5 μg of alfacalcidol) were administered orally as a single dose to healthy adult men (n=20) under fasting conditions in a crossover design to measure each 1α, $25(OH)_2D$* concentration in serum. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed. The analysis results confirmed the bioequivalence of these drugs. (based on PAB/PCD Notification No. 718, May 30, 1980)[1].

(Note) A single oral dose of 5 μg is unapproved.

*1α, $25(OH)_2D$: Active metabolite, 1α, $25(OH)_2D_3$ of Alfacalcidol + Biological origin, 1α, $25(OH)_2D_2$



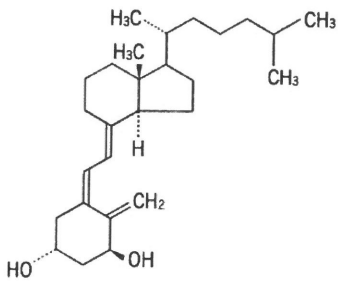
	Determined parameter		Reference parameter
	AUC_{48} (pg·hr/mL)	Cmax (pg/mL)	Tmax (hr)
ALFACALCIDOL CAPSULES 1μg "TOWA" (Capsules, 5μg)	2807.2±591.9	87.1±22.0	8.7±2.6
Reference drug (Capsules, 5μg)	2693.4±687.3	84.3±23.6	9.3±2.4

(Mean ± S.D., n=20)

Serum concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

PHYSICOCHEMICAL PROPERTIES

Structural formula:



Nonproprietary name:
Alfacalcidol

Chemical name:
(5*Z*, 7*E*)-9,10-Secocholesta-5,7,10 (19)-triene-1α, 3β-diol

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

Molecular weight:
400.64

Description:
Alfacalcidol occurs as white crystals or crystalline powder. It is freely soluble in methanol, ethanol (99.5), chloroform, and dichloromethane, soluble in acetone and diethyl ether, and practically insoluble in water and hexane. It is affected by air and by light.

Melting point:
137 - 142°C (Ergocalciferol measurement, JP)

**/* PRECAUTIONS FOR HANDLING

**/* Stability test

In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months),

ALFACALCIDOL CAPSULES 0.25μg, 0.5μg, and 1μg "TOWA" were estimated to be stable for 3 years under normal distribution conditions[4)5)6)].

PACKAGING

ALFACALCIDOL CAPSULES 0.25μg "TOWA":
Boxes of 100 capsules, 1,000 capsules (PTP)
ALFACALCIDOL CAPSULES 0.5μg "TOWA":
Boxes of 100 capsules, 1,000 capsules (PTP)
ALFACALCIDOL CAPSULES 1μg "TOWA":
Boxes of 100 capsules, 1,000 capsules (PTP)

REFERENCES

1) Internal data of Towa Pharmaceutical Co., Ltd.:
Bioequivalence test (capsules 0.25μg)
2) Internal data of Towa Pharmaceutical Co., Ltd.:
Bioequivalence test (capsules 0.5μg)
3) Internal data of Towa Pharmaceutical Co., Ltd.:
Bioequivalence test (capsules 1μg)
4) Internal data of Towa Pharmaceutical Co., Ltd.:
Stability test (capsules 0.25μg)
5) Internal data of Towa Pharmaceutical Co., Ltd.:
Stability test (capsules 0.5μg)
6) Internal data of Towa Pharmaceutical Co., Ltd.:
Stability test (t capsules 1μg)

Manufacturer and Distributor
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