- Active Vitamin D₃ for Treatment of Psoriasis vulgaris -

**JP Tacalcitol Ointment Bonalfa®**
**High Ointment 20 µg/g**

**JP Tacalcitol Lotion Bonalfa®**
**High Lotion 20 µg/g**

**< Tacalcitol Hydrate preparation >**

Powerful drug and Prescription drug

<table>
<thead>
<tr>
<th>Storage</th>
<th>Ointment</th>
<th>Lotion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store at room temperature in a tight and light-resistant container.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Expiration date</th>
<th>Ointment</th>
<th>Lotion</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years from the date of production (The expiration date is indicated on the outer package.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONTRAINDICATIONS (BONALFA High Ointment 20 µg/g and BONALFA High Lotion 20 µg/g are contraindicated in the following patients.)**

Patients with a history of hypersensitivity to any of the ingredients of BONALFA High

**DESCRIPTION**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>BONALFA High Ointment 20 µg/g</th>
<th>BONALFA High Lotion 20 µg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Tacalcitol Hydrate</td>
<td>Tacalcitol Hydrate</td>
</tr>
<tr>
<td>Content (per 1g)</td>
<td>20.87 µg (20 µg as tacalcitol: 0.002%)</td>
<td></td>
</tr>
</tbody>
</table>

**Inactive ingredients**

- White petrolatum, Liquid paraffin, another ingredient
- Tocopherol, Stearyl alcohol, Polyoxymethylene hydrogenated castor oil 60, Glyceryl monostearate, ene glycol, Methyl parahydroxybenzoate, Propyl parhydroxybenzoate, Sodium citrate, Xanthan gum, Mono- basic potassium phosphate, Di basic sodium phosphate, and 6 other ingredients.

<table>
<thead>
<tr>
<th>pH</th>
<th>7.0-8.0</th>
</tr>
</thead>
</table>

**Color/Description**

- White to slightly yellow, odorless ointment
- White emulsified lotion

**INDICATIONS**

Psoriasis vulgaris

**DOSAGE AND ADMINISTRATION**

Apply adequate amount of BONALFA High to the affected area, usually once a day.

**PRECAUTIONS**

1. **Careful Administration (BONALFA High Ointment 20 µg/g and BONALFA High Lotion 20 µg/g should be administered with care in the following patients.)**

Patients with renal dysfunction [Serum calcium values may be increased.]

2. **Important Precautions**

(1) Since BONALFA High is active vitamin D₃ preparation, usage of BONALFA High may cause serum calcium level to increase. Because hypercalcemia may reduce renal function, when BONALFA High is used in any of the following patients, tests on serum calcium, urine calcium and renal function (creatinine, BUN, etc.) should be performed periodically (once after 2 to 4 weeks of the initial administration, and when needed by physician's judgment afterward). If any abnormality in these test results is observed, administration of BONALFA High should be discontinued, and patient's condition should be monitored. (See “Clinically significant adverse reactions”. About the symptoms of hypercalcemia, see “Overdos age.”.)

1) Patients who use nearly 10g/day for widespread eruption, etc., and those who may have increased percutaneous absorption due to reduced
skin barrier ability because of high severity of eruption

2) Patients with renal dysfunction

3) Patients who are administrated any drug with suspicion of interaction with BONALFA High, and those who had been treated with cyclosporine before the initiation of BONALFA High (See “Drug Interactions”).

(2) The effect of BONALFA High is usually manifesting itself by the 6th week after the initiation of administration. Patient’s condition should be carefully monitored, and if symptomatic improvement is not observed, the administration should be discontinued.

(3) The safety of BONALFA High in Occlusive Dressing Therapy (ODT) has not been established. (Subjects are prone to skin irritation. The transcutaneous absorption tends to be promoted compared with a simple application, and systemic adverse reactions may be inclined to occur.)

3. Drug Interactions

Precautions for concomitant use of medications (BONALFA High Ointment 20 μg/g and BONALFA High Lotion 20 μg/g should be administered with care when concomitantly used with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>Increased serum calcium level may occur.</td>
<td>Thiazide diuretics may decrease urinary calcium excretion and increase serum calcium level.</td>
</tr>
<tr>
<td>Calcium containing preparations (e.g., Calcium lactate hydrate, Precipitated calcium carbonate)</td>
<td>Increased serum calcium level may occur.</td>
<td>BONALFA High promotes the intestinal absorption of calcium.</td>
</tr>
<tr>
<td>Vitamin D and its derivatives (e.g., Alfacalcidol, Calcitriol, Calciotin, Maxacalcitol)</td>
<td>Increased serum calcium level may occur.</td>
<td>Additive effect</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Increased serum calcium level may occur.</td>
<td>Cyclosporine-induced renal dysfunction may increase serum calcium level.</td>
</tr>
</tbody>
</table>

4. Adverse Reactions

For BONALFA High Ointment 20 μg/g, 38 events of subjective and/or objective adverse reactions were reported in 24 (4.2%) of the 567 cases evaluated for safety in the clinical trials for approval and additional indication approval. Major symptoms were 10 events of irritation (1.8%), 9 events of itching (1.6%), 7 events of feeling irritated (1.2%), 7 events of redness (1.2%) and 4 events of swelling (0.7%), etc. Abnormal laboratory test values as adverse reactions observed were 6 events of intact PTH decreased in 166 cases (3.6%), etc. In the subjects who concomitantly used thiazide diuretics, 1 event in 14 cases (7.1%) of urine calcium increased and 1 event in 542 cases (0.2%) of serum calcium increase observed. (At the time of approval for additional indication of BONALFA High Ointment 20 μg/g)

In the post-marketing specified drug-use survey, 35 events of adverse reactions (including abnormal laboratory test values) were reported in 26 (3.3%) of the 783 cases evaluated for safety. Major adverse reactions were 9 events of redness (1.1%) and 8 events of irritation (1.0%), etc. (At the completion of Reexamination for BONALFA High Ointment 20 μg/g and BONALFA High Lotion 20 μg/g)

For BONALFA High Lotion 20 μg/g, 10 events of subjective and/or objective adverse reactions were reported in 8 (10.5%) of the 76 cases evaluated for safety. Reported symptoms were 2 events of irritation (2.6%), 2 events of feeling irritated (2.6%), 2 events of itching (2.6%), 2 events of redness (2.6%), 1 event of pigment (1.3%) and 1 event of contact dermatitis (1.3%). There were no abnormal laboratory test values considered to be adverse reactions. Comparison study between BONALFA High Lotion 20 μg/g and BONALFA High Ointment 20 μg/g did not show difference in the incidences of adverse reactions between these dosage forms.11,21 (At the time of approval of BONALFA High Lotion 20 μg/g)

(1) Clinically significant adverse reactions

Hypercalcemia (Incidence unknown): Hypercalcemia and related symptoms (malaise, anorexia, etc.) may occur. If any abnormality is observed, administration of BONALFA High should be discontinued, and biochemical tests (serum calcium, urine calcium, etc.) should be conducted. Necessary measures such as fluid infusion should be taken. (See “Important Precautions”)

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence/Organ system</th>
<th>Incidence unknown(a)</th>
<th>≥ 1%</th>
<th>&lt; 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychoneurologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologic(b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) Note 1: Headache

(b) Note 2: Iritation, itching, feeling irritated, redness, Swelling, pigmentation, contact dermatitis

AST (GOT) increased, LDH increased, ALP increased

ALT (GPT) increased
Electrolyte | Urine calcium increased | Serum calcium increased, serum phosphate decreased
--- | --- | ---
Endocrine | | Intact PTH decreased
Renal | | Urinary protein positive, serum creatinine increased
Blood | White blood cell increased

Note 1) The events reported for BONALFA Ointment 2 μg/g, BONALFA Cream 2 μg/g or BONALFA Lotion 2μg/g.

Note 2) Discontinue the administration of BONALFA High if the adverse reactions occur severely.

5. Use in the Elderly
Since elderly patients often have reduced physiological function, care to avoid overdose should be taken.

6. Use during Pregnancy, Delivery or Lactation
(1) BONALFA High should not be used in large amounts or long term over large areas in pregnant women or women suspected of being pregnant. [The safety of BONALFA High has not been established in pregnant women.]

(2) Breast feeding should be avoided during treatment with BONALFA High. [Animal studies (in rats) have shown that this drug is secreted in breast milk.]

7. Pediatric Use
The safety of BONALFA High in low birth weight infants, newborn infants, nursing infants, small children and children has not been established. [No clinical experience]

8. Overdosage
Hypercalcemia may occur as a result of application of BONALFA High exceeding 10 g/day (200 μg/day as tacalcitol).

**Signs and symptoms:** The main symptoms of hypercalcemia are malaise, feeling of weakness, anorexia, nausea, vomiting, enlarged feeling of abdomen, abdominal pain, headache, dizziness, myalgia and muscular weakness, etc.

**Treatment:** Discontinue administration of BONALFA High promptly. Biochemical tests (serum calcium, urine calcium, etc.) should be performed and necessary measures such as fluid infusion should be taken. (See “Important Precautions”)

9. Precautions concerning Use
(1) **Application site:** Do not apply BONALFA High to the cornea or the conjunctiva for ophthalmic use.

(2) **At use:** Do not touch the skin area of epidermal loss, with the hand exposed to BONALFA High.

**PHARMACOKINETICS**

1. **Healthy adult males**
When a single or 5-day repeated dose of 120, 160 or 200 μg/day of tacalcitol was applied in the form of ointment (8 to 24 μg/g) to healthy adult males (single dose in 18 subjects, repeated dose in 6 subjects), the serum and urinary levels of unchanged compound were less than the quantitation limit in all subjects. 3)

2. **Patients with psoriasis vulgaris**
When 140 or 200 μg/day of tacalcitol was applied in the form of ointment (20 μg/g) to psoriasis vulgaris patients for 28 days, the unchanged compound was detected in the serum of 5 of 7 patients and 4 of 7 patients, respectively, at 4 hours after application. However, the serum levels of neither dosage group exceeded the quantitation limit at 24 hours after application. The urinary unchanged compound levels were also below the quantitation limit in all patients at 24 hours after application.

After applying 200 μg/day of tacalcitol in the form of ointment (20 μg/g) or lotion (20 μg/g) to psoriasis vulgaris patients for 8 days, its transfer to blood was compared between the dosage forms. In the lotion group, the unchanged compound was detected in the serum of 1 of 8 patients at 12 hours after application. In the ointment group, it was detected in the serum of 4 of 7 patients at 4 hours and/or 12 hours after application. On the 1st and the 8th day of the treatment with both dosage forms, the levels of unchanged compound were below the quantitation limit in all patients for 28 days.

(Reference Information)
BONALFA High Ointment 20 μg/g and BONALFA High Lotion 20 μg/g are the higher concentration products containing 10-fold of active ingredient (tacalcitol hydrate) than BONALFA Ointment 2 μg/g and BONALFA Lotion 2 μg/g which have been already used clinically, and the formula of the other ingredients such as base ingredient are not changed.

The ointment forms with various concentrations of tacalcitol hydrate were prepared and their absorption and metabolism were investigated in rats, in which concentration-dependent pharmacokinetic parameters were observed. Therefore, the disposition of BONALFA High following absorption (distribution, metabolism and excretion) was considered to be equivalent with those of BONALFA Ointment 2 μg/g.

(1) **Absorption**
When ointment including 3H-labeled tacalcitol hydrate was transcutaneously administered to rats, plasma radio-
activity levels reached its peak at 2 hours after application and decreased thereafter.\(^6\)

When ointment including \(^{3}H\)-labeled tacalcitol hydrate (2 to 40 \(\mu g/g\) as tacalcitol hydrate) was transcutaneously administered to rats, the plasma Cmax and AUC of the unchanged compound were increased concentration-dependently.\(^6\)

(2) Distribution
After transcutaneous administration (24 hrs application) of ointment including \(^{3}H\)-labeled tacalcitol hydrate to rats, a high concentration of the unchanged compound was found in the skin of application site. The radioactivity was also found in relatively high in the liver and small intestine tissues.\(^5\)

(3) Metabolism
After subcutaneous administration of \(^{3}H\)-labeled tacalcitol hydrate to rats and dogs as well as transcutaneous administration (24 hrs application) of ointment including \(^{3}H\)-labeled tacalcitol hydrate to rats, the unchanged compound and its metabolite, 1α,24(R)25-(OH)\(_2\)D\(_3\), were found in the plasma.\(^5,7,8\)

When ointment including \(^{3}H\)-labeled tacalcitol hydrate (2-40 \(\mu g/g\) as tacalcitol hydrate) were transcutaneously applied to rats, no difference in metabolism was observed among different concentrations.\(^6\)

(4) Excretion
After subcutaneous administration of \(^{3}H\)-labeled tacalcitol hydrate to rats and dogs, approximately 15% of the dose administered was excreted in the urine, and approximately 80% was excreted in the feces during 10 days following administration in the rats and during 11 days in the dogs.\(^7,8\)

After transcutaneous administration of ointment including \(^{3}H\)-labeled tacalcitol hydrate as a single dose (24 hrs application) or repeated dose for 7 days to rats, approximately 30% of the dose administered was excreted in the urine and feces during 11 days following the single dose and up to 6 days after the final dose of repeated administration. Similar to subcutaneous administration, it was found to be excreted mainly in the feces.\(^7\)

CLINICAL STUDIES
The efficacy of BONALFA High Ointment 20 \(\mu g/g\) was evaluated in a comparison study with BONALFA Ointment 2 \(\mu g/g\) conducted in 34 centers in patients with psoriasis vulgaris whose intractable eruption had not been sufficiently improved by 4-week treatment with BONALFA Ointment 2 \(\mu g/g\). The efficacy rate of BONALFA High Ointment 20 \(\mu g/g\) judged to be “moderately improved” or better was 86.4% (51/59 cases).\(^9\) In another study on steroid-resistant eruption conducted in 31 centers in patients with psoriasis vulgaris whose intractable eruption had not been sufficiently improved by 3-week treatment of steroid external preparation,

BONALFA High Ointment 20\(\mu g/g\) showed the efficacy rate of 88.9% (48/54 cases).\(^10\)

The efficacy of BONALFA High Lotion 20 \(\mu g/g\) was evaluated in a comparison study with BONALFA High Ointment 20 \(\mu g/g\) conducted in 30 centers in patients with psoriasis vulgaris whose intractable eruption had not been sufficiently improved by 4-week treatment of other external therapy or had been judged as intractable according to his/her treatment history, the degree of eruption, etc. The efficacy rates of improvement judged to be “moderately improved” or better were 71.9% (41/57 cases) and 73.0% (46/63 cases) for BONALFA High Lotion 20 \(\mu g/g\) and BONALFA High Ointment 20 \(\mu g/g\), respectively, showing equivalent efficacy in both dosage forms.\(^7\)

In a clinical study of BONALFA High Ointment 20 \(\mu g/g\) conducted in 9 centers in patients whose psoriasis vulgaris was judged as non-intractable according to his/her treatment history, the degree of eruption, etc., the efficacy rate of BONALFA Ointment 20 \(\mu g/g\) was 91.2% (62/68 cases).\(^11\)

PHARMACOLOGY
1. Anti-inflammatory activity on skin
Tacalcitol showed concentration-dependent inhibition of IL-8 production, which is inflammatory cytokine, in cultured human epidermal cells.\(^12\)

When applied to the skin of hairless mice where inflammation had been elicited by 12-O-tetradecanoylphorbol-13-acetate (TPA), tacalcitol inhibited neutrophil infiltration (measured myeloperoxidase (MPO) activity as an index).\(^13\) Ointment (including 20 \(\mu g/g\) as tacalcitol) showed similar activity.\(^14\)

Ointment (including 20 \(\mu g/g\) as tacalcitol) significantly improved the inflammatory change of skin elicited by 12-O-tetradecanoylphorbol-13-acetate (TPA) in hairless mice.\(^14\)

2. Inhibitory activity on proliferation of epidermal cells
Tacalcitol showed inhibition of DNA synthesis and cell proliferation in cultured mouse epidermal cells, as well as in cultured human epidermal cells obtained from the normal area and psoriasis-affected area.\(^15,16\)

When applied to the epidermis of hairless mice where cell proliferation had been stimulated by 12-O-tetradecanoylphorbol-13-acetate (TPA), tacalcitol was found to inhibit ornithine decarboxylase (ODC) activity, which is an index of cell proliferation. Ointment (including 20 \(\mu g/g\) as tacalcitol) showed similar activity.\(^14\)

Inhibitory effects of ODC activity were found equivalent in ointment vs lotion.\(^17\)

After 4-week treatment of psoriasis patients with BONALFA Ointment 2 \(\mu g/g\), DNA synthesis and mitosis of epidermal cells were inhibited. The number of S-phase cells decreased, and proliferation of the epidermal cells was inhibited.\(^18\)
3. Differentiation-inducing activity on epidermal cells
Tacalcitol promoted the formation of an intracellular insoluble membrane (cornified envelope), which is necessary for keratogenesis and increased transglutaminase (TGase) activity in mouse epidermal cell cultures. Tacalcitol increased the synthesis of involucrin, a precursor protein of the intracellular insoluble membrane, in normal human epidermal cell cultures. Ointment (including 20 μg/g as tacalcitol) increased TGase activity in the epidermis of hairless mice. In addition, electron microscopic examination of the affected skin of psoriasis patients after application of BONALFA Ointment 2 μg/g showed keratin-pattern formation in corneum and formation of keratohyaline-containing granular layers, suggesting normalized keratogenesis.

4. Affinity for the 1α,25-(OH)2D3-specific receptor in epidermal cells
Tacalcitol has high affinity for 1α,25-(OH)2D3-specific receptors in mouse and normal human epidermal cells.

PHYSICOCHEMISTRY
Nonproprietary name: Tacalcitol Hydrate (JAN)
Chemical name: (1S,3R,5Z,7E,24R)-9,10-Secocholesta-5,7,10(19)-triene-1,3,24-triol monohydrate
Structural formula:

\[
\text{\begin{figure}}
\end{figure}}
\]

Molecular formula: C29H44O3·H2O
Molecular weight: 434.65
Melting Point: approximately 100°C
Description: Tacalcitol hydrate occurs as white crystal or crystalline powder. It is very soluble in methanol or ethanol (99.5%), and practically insoluble in water. It is decomposed by light.

PACKAGING
Ointment
10 g x 1 tube, 10 g x 10 tubes (aluminum tubes)
Lotion
10 g x 1 container, 10 g x 10 containers (plastic containers)

REFERENCES
1) Internal Report: Pharmacokinetics (psoriasis vulgaris patients), 2005
2) High-concentration TV-02 Lotion Clinical Study Group (Psoriasis): Nishinihon Journal of Dermatology, 68 (4) 426, 2006
3) Internal Report: Safety confirmatory study (healthy adults), 2001
4) High-concentration TV-02 Ointment Clinical Study Group (Psoriasis): Nishinihon Journal of Dermatology, 64 (2) 237, 2002
5) Ohta T. et al.: Xenobiotic Metabolism and Disposition, 5 (1) 39, 1990
6) Internal Report: Time course of plasma concentration (rats), 2002
7) Ohta T. et al.: Xenobiotic Metabolism and Disposition, 5 (1) 3, 1990
8) Ohta T. et al.: Xenobiotic Metabolism and Disposition, 5 (1) 63, 1990
9) High-concentration TV-02 Ointment Clinical Study Group (Psoriasis): Nishinihon Journal of Dermatology, 64 (1) 105, 2002
11) Internal Report: Open clinical study (psoriasis vulgaris patients, 2007
12) Internal Report: Effect on IL-8 production (normal human epidermal cells), 1999
17) Internal Report: Inhibitory activity on proliferation of epidermal cells (TPA-applied hairless mice), 2003

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Sales Training & Information Department
TEIJIN PHARMA LIMITED
2-1, Kasumigaseki 3-chome, Chiyoda-ku, Tokyo 100-8585
Toll-Free: 0120-189-315
The Internal Reports are also available at the address.

Manufactured and Distributed by
TEIJIN PHARMA LIMITED
2-1, Kasumigaseki 3-chome, Chiyoda-ku, Tokyo