Approval date: 2024.11.22 Revised: 2024.12.25; 2025.01.17;2025.04.08

Zedman®

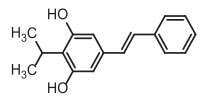
Prescribing information for Zedman®

Topical

Please read the instructions carefully and use under the guidance of a physician or pharmacist.

[Drug Name]
Generic Name: Tapinarof Cream
Chinese Pinyin: Benweimode Rugao

[Ingredients]
The active ingredient of this product is tapinarof.
Chemical Name: (E)-2-isopropyl-5-styrylbenzene-1,3-diol
Chemical structure:



Molecular formula: C17H18O2
Molecular weight: 254.32
Excipients: White petrolatum, Cetearyl alcohol, Ceteth-20 (or Polyethylene glycol cetyl ether), Medium-chain triglycerides (MCT), Glyceryl mono- and distearate, Butylated hydroxytoluene (BHT), Ethylparaben, Polysorbate 80, Diethylene glycol monoethyl ether, Propylene glycol, Disodium edetate (or Disodium EDTA), Citric acid, Sodium citrate and Purified water.

[Dosage Form]
White to off-white cream.

[Indication]
Zedman® is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

[Dosage Form]
1% (15g: 0.15g)

[Usage]
For topical use, apply twice daily, once in the morning and once in the evening. Spread evenly over the affected area to form a thin layer.
Avoid exposure to sunlight after applying the product to the affected skin. Measures to avoid light are necessary even under natural light.
The safety and efficacy of continuous use of this product for more than 8 weeks have not been established. The total duration of continuous clinical use must not exceed 8 weeks.
This product must not be used in the mouth, eyes, or vagina.

[Adverse Reactions]
Since clinical trials are conducted under varying conditions, adverse reaction rates observed in a clinical trial for one drug cannot be directly compared to those of another drug and may not reflect actual adverse reaction rates in practice.
In a randomized, double-blind, placebo-controlled confirmatory clinical trial, 271 patients aged 2 years and older with atopic dermatitis were treated with tapinarof cream or placebo twice daily over a 56-day period. Results showed that approximately 22.4% of patients experienced drug-related adverse reactions. Common adverse reactions included folliculitis, contact dermatitis, application site pruritus, application site pain, and atopic dermatitis. Most reactions were transient and mild to moderate in severity, occurring primarily within the first 14 days of treatment. The majority of local cutaneous adverse reactions resolved spontaneously without intervention. For details, see Table 1.
Systemic adverse reactions and reactions affecting other organ systems were rare. Observed adverse reactions included tinea corporis, furuncle, application site swelling, application site papules, abnormal hair growth, skin pain, miliaria, elevated alanine aminotransferase (ALT), increased basophil count, increased eosinophil count, increased leukocyte count, hyperuricemia, allergic rhinitis, and supraventricular extrasystole. No deaths occurred during the trial. One severe adverse reaction (allergic dermatitis) was reported in 1 patient (0.5%) during the study.

Table 1: Adverse Reactions Occurring in ⩾1% of subjects

Adverse Reactions (%)	Tapinarof cream N=183	Placebo N=88
Folliculitis[a]	7.1	3.4
Contact dermatitis[b]	3.8	3.4
Application site pruritus	3.3	1.1
Application site pain	3.3	0
Atopic dermatitis	1.1	0

a Folliculitis includes application site folliculitis and folliculitis.

b Contact dermatitis includes contact dermatitis and allergic dermatitis.

Adverse reactions leading to treatment discontinuation in >1% of subjects who received tapinarof cream were allergic dermatitis (1.6%) and contact dermatitis (1.1%).

[Contraindications]
Patients who are allergic to tapinarof or any other ingredients in the cream are contraindicated.

[Precautions]
1.For topical cutaneous use only. Do not use occlusive dressings.
2.Tighten the cap securely after each use.
3.Discontinue use if the product shows signs of deterioration.
4.During treatment, physicians should advise patients to avoid exposure to natural or artificial light after application or to adopt photoprotective measures.
5.Avoid application to mucous membranes, ulcers, or severely compromised skin.
6.If accidental eye contact occurs, flush immediately with copious amounts of water.
7.Wash hands after application unless the hands are the treatment site.

[Pregnancy and Lactation]
Clinical trials have not been conducted in pregnant or breastfeeding women, and the safety of this product has not been established. Pregnant women, women planning pregnancy, and breastfeeding women should use this product with caution. For animal data, refer to the [Pharmacology and Toxicology] section.

[Pediatric Use]
Data from a randomized, double-blind, placebo-controlled confirmatory clinical trial (including 142 pediatric subjects aged 2–17 years) support the efficacy and safety of tapinarof cream applied twice daily in children aged 2 years and older with mild to moderate atopic dermatitis. For details, refer to the [Clinical Trials] section.
The efficacy and safety of tapinarof cream in children under 2 years of age have not been established.

[Geriatric Use]
Clinical studies of tapinarof cream did not include a sufficient number of subjects aged 65 years and older to determine whether they respond differently compared to younger patients.
Elderly patients requiring treatment with this product should use it under the guidance of a healthcare professional.

[Drug Interaction]
Tapinarof is not an inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5. Tapinarof is not an inducer of CYP1A2, CYP2B6 or CYP3A4. Tapinarof is not an inhibitor of BCRP, MATE1, MATE-2K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, or P-gp. Tapinarof is not a substrate for BCRP, OATP1B1, OATP1B3, or P-gp. Therefore, the risk of drug interactions caused by tapinarof is minimal.

[Overdose]
No overdose case has been reported.

[Clinical Pharmacology]
Mechanism of Action
Refer to the [Pharmacology and Toxicology] section.
Pharmacodynamics
Pharmacodynamics of tapinarof cream are unknown.
Pharmacokinetics
Absorption: Based on multiple published clinical pharmacokinetic studies, topical application of 1% tapinarof cream in healthy adult volunteers or patients with atopic dermatitis showed that tapinarof acts locally on the skin, with minimal systemic exposure. Systemic exposure was not correlated with drug concentration, dose, or frequency of application, and no significant accumulation was observed with repeated use.
A clinical study in generalized atopic dermatitis patients aged 2–17 years confirmed that the pharmacokinetic profile of tapinarof is independent of age and disease status. In pediatric patients aged 2–17 years, even at the maximum usage amount (affected skin area ranging from 26% to 90%, with a mean of 43%), systemic exposure to tapinarof was minimal or below quantifiable levels, similar to the pharmacokinetic profile observed in adults, indicating a low systemic safety risk.
During clinical studies of tapinarof cream, blood concentrations of tapinarof were monitored in pediatric subjects. Results showed that all plasma samples had tapinarof concentrations below the lower limit of quantification (0.1 ng/mL). Systemic exposure in pediatric patients was minimal, and no systemic accumulation was observed with repeated topical application. These findings are consistent with previously published pharmacokinetic data in both adult and pediatric atopic dermatitis patients.
Distribution: In vitro studies indicate that the plasma protein binding rate of tapinarof is approximately 99%.
Metabolism: In vitro studies demonstrate that tapinarof undergoes multiple metabolic pathways in the liver, including oxidation, glucuronidation, and sulfation.
Excretion: Animal studies show that after subcutaneous injection, tapinarof is primarily excreted via feces (72%–78%) and urine (11%–17%).
Pharmacogenetics
No related study has been conducted on tapinarof.

[Clinical Studies]
A confirmatory, randomized, double-blind, placebo-controlled trial was conducted, in which 271 patients aged 2 years and older with atopic dermatitis were randomly assigned in a 2:1 ratio to receive either the tapinarof or placebo twice daily for 56 days.
At baseline, the Investigator's Global Assessment (IGA) score for subjects ⩾3, with 92.3% (250 subjects) having an IGA score of 3 and 7.7% (21 subjects) having an IGA score of 4. The baseline Eczema Area and Severity Index (EASI) scores ranged from 3.0 to 34.5, with 21.8% (59 subjects) having EASI scores between 1.1 and 7.0, 73.0% (198 subjects) between 7.1 and 21.0, and 5.2% (14 subjects) with scores of 21.1 or higher.
The primary efficacy endpoint was the percentage of subjects achieving at least a 75% reduction in EASI score from baseline at Day 56 (EASI 75 response rate). The key secondary efficacy endpoint was the percentage of subjects achieving an IGA score of clear (0) or almost clear (1) with a reduction of at least 2 grades from baseline at Day 56 (IGA response rate).
Efficacy results: The point estimate for efficacy in the tapinarof group was superior to that in the placebo group. The point estimate for the difference between groups in the primary efficacy endpoint was 28.9%, and the point estimate for the difference in the key secondary efficacy endpoint was 24.9%. The results for the primary and key secondary efficacy endpoints across different age groups are shown in the following table (Table 2).

Table 2: The results for the primary and key secondary efficacy endpoints across different age groups

Clinical Response	Tapinarof cream	Placebo
Pediatric Subjects (2-17 years)		
N	96	46
EASI 75 response rate (%)	69.2	31.0
IGA response rate (%)	61.5	28.6
Adult Subjects (⩾18 years)		
N	87	42
EASI 75 response rate (%)	38.0	19.5
IGA response rate (%)	29.3	13.5

[Pharmacology and Toxicology]
Pharmacology
Tapinarof is an aryl hydrocarbon receptor (AhR) agonist. The specific mechanisms by which tapinarof cream exerts its therapeutic actions are unknown.
Toxicology Studies
Tapinarof showed negative results in the following genotoxicity tests:
Ames test, Chromosomal aberration test in Chinese hamster lung (CHL) cells, Chromosomal aberration test in Chinese hamster ovary (CHO) cells, In vitro mutation assay at the thymidine kinase (TK) locus in L5178Y mouse lymphoma cells, In vivo micronucleus test in mice, In vivo micronucleus test in rats.
Reproductive toxicity
In the fertility and early embryonic development toxicity study in rats, subcutaneous administration of tapinarof at 30 mg/kg/day to both male and female rats (approximately 268 times the maximum recommended human dose [MRHD] based on AUC) showed no effect on fertility.
In the rat embryo-fetal development toxicity study, pregnant rats were administered tapinarof subcutaneously at doses of 1.2, 6.9, and 34 mg/kg/day during the organogenesis period. An increased incidence of fetal skeletal variations (nasal bone abnormalities) was observed at the 34 mg/kg/day dose (268 times the MRHD based on AUC), with no tapinarof-related fetal deaths or malformations noted.
In the rabbit embryo-fetal development toxicity study, pregnant rabbits were administered tapinarof subcutaneously twice daily at doses of 0.3, 1.0, and 3.0 mg/kg/day during the organogenesis period. At the 3.0 mg/kg/day dose (30 times the MRHD based on AUC), decreased maternal weight gain and increased implantation loss were observed, along with fetal skeletal variations. No tapinarof-related embryo-fetal deaths or fetal malformations were seen at the 1 mg/kg/day dose (16 times the MRHD based on AUC), and no tapinarof-related fetal malformations were observed at the 3 mg/kg/day dose (30 times the MRHD based on AUC).
In another rabbit embryo-fetal development toxicity study, pregnant rabbits were administered tapinarof subcutaneously at doses of 1, 2, and 3 mg/kg/day during the organogenesis period. No tapinarof-related embryo-fetal deaths or fetal malformations were observed at the 3 mg/kg/day dose (20 times the MRHD based on AUC).
In the rat perinatal toxicity study, rats were administered tapinarof subcutaneously from gestation day 6 to lactation day 20 at doses of 1, 6, and 30 mg/kg/day. At the 30 mg/kg/day dose (268 times the MRHD based on AUC), decreased maternal food consumption and weight gain were observed. Reduced fetal survival and fetal weight were seen at doses >6 mg/kg/day (45 times the MRHD based on AUC). No effects on fetal survival and viability were noted at the 1 mg/kg/day dose (6 times the MRHD based on AUC). Up to the highest dose of 30 mg/kg/day (268 times the MRHD based on AUC), no effects on postnatal development, neurobehavioral function, or survival of the offspring were observed. Additionally, tapinarof was detectable in the plasma of offspring from the 6 and 30 mg/kg/day dose groups 10 days after birth, suggesting that tapinarof is excreted in maternal rat milk.
Carcinogenicity
In CD-1 mice, topical application of tapinarof cream (0.5%, 1.5%, and 3%) was administered daily for 98 weeks in females and 102 weeks in males. The highest dose, based on AUC, was approximately 44 times the maximum recommended human dose (MRHD). No tapinarof-related carcinogenicity was observed.
In Wistar Han rats, subcutaneous injection of tapinarof at 1 mg/kg/day (approximately 9 times the MRHD based on AUC) was administered to females for 83 weeks. No tapinarof-related carcinogenicity was observed.
Juvenile Animal Toxicity
In juvenile rats, tapinarof was administered via subcutaneous injection at doses of 1, 10, and 20 mg/kg/day from postnatal day 7 to day 21, and at doses of 1.5, 15, and 30 mg/kg/day from postnatal day 22 to day 77. At doses ⩾15 mg/kg/day (approximately 165 times the MRHD based on AUC), renal pelvis dilation was observed. No adverse effects were observed at the dose of 1.5 mg/kg/day (approximately 11 times the MRHD based on AUC).

[Storage] Avoid exposure to light, keep sealed, store at a temperature not exceeding 30°C, do not freeze. Keep tapinarof cream out of the reach of children.

[Package]Aluminum medicinal ointment tube. 15g per tube, 1 tube per box.

[Validity period] 24 months.

[Implementation Standards] YBH27302024

[Approval No.] 国药准字H20240040

[Marketing Authorization Holder]
Name: Shanghai Thederma Pharmaceutical Co., Ltd.
Registered Address: Building 3&4, No. 865, Zuchongzhi Road, Pudong New District, Shanghai
Post code: 201210
Phone number: 021-60191662
Fax Number: 021-60191661-601
Website: http://www.thederma.com

[Manufacturing Company]
Company Name: Shanghai New Asia Pharmaceutical Co., Ltd.
Address: No. 1500 Kunyang Road, Minhang District, Shanghai
Post code: 200245
Phone number: 021-54722105
Fax Number: 021-54726604

THEDERMA 泽立美®