

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use WYNZORA Cream safely and effectively. See full prescribing information for WYNZORA Cream.

WYNZORA® (calcipotriene and betamethasone dipropionate) cream, for topical use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

WYNZORA Cream is a combination of calcipotriene, a vitamin D analog, and betamethasone dipropionate, a corticosteroid, indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Apply WYNZORA Cream to affected areas once daily for up to 8 weeks. (2)
- Discontinue therapy when control is achieved. (2)
- Do not use more than 100 g per week. (2)
- Do not use with occlusive dressings unless directed by a physician. (2)
- Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Cream: 0.005%/0.064% (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- **Hypercalcemia and Hypercalciuria:** Hypercalcemia and hypercalciuria have been observed with use of topical calcipotriene. If either occurs, discontinue until parameters of calcium metabolism normalize. (5.1)
- **Effects on Endocrine System:** Can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency during and after withdrawal of treatment. Risk factors include the use of high-potency topical corticosteroid, use over a large surface area, or to areas under occlusion, prolonged use, altered skin barrier, liver failure, and young age. Modify use should HPA axis suppression develop. (5.2)
- **Ophthalmic Adverse Reactions:** May increase the risk of cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist. (5.5)

ADVERSE REACTIONS

The most common adverse reactions reported by more than 1% of subjects treated with WYNZORA Cream were upper respiratory infection, headache, and application site irritation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EPI Health, LLC at 1-800-644-8240 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hypercalcemia and Hypercalciuria
- 5.2 Effects on Endocrine System
- 5.3 Allergic Contact Dermatitis with Topical Corticosteroids
- 5.4 Allergic Contact Dermatitis with Topical Calcipotriene
- 5.5 Ophthalmic Adverse Reactions

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

WYNZORA Cream is indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

Apply WYNZORA Cream to affected areas once daily for up to 8 weeks. Rub in gently to ensure that the plaques are saturated with the cream.

Do not use more than 100 g per week.

Discontinue therapy when control is achieved.

Do not use:

- with occlusive dressings unless directed by a healthcare provider
- on the face, groin, or axillae, or if skin atrophy is present at the treatment site

WYNZORA Cream is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Cream: 0.005%/0.064%.

Each gram of WYNZORA Cream contains 50 mcg of calcipotriene and 0.644 mg of betamethasone dipropionate in a white cream.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercalcemia and Hypercalciuria

Hypercalcemia and hypercalciuria have been observed with use of topical calcipotriene. If hypercalcemia or hypercalciuria develop, discontinue treatment until parameters of calcium metabolism have normalized.

5.2 Effects on Endocrine System

Hypothalamic-Pituitary-Adrenal Axis Suppression

WYNZORA Cream can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age.

Evaluation for HPA axis suppression may be done by using the adrenocorticotrophic hormone (ACTH) stimulation test. If HPA axis suppression is documented, gradually withdraw WYNZORA Cream, reduce the frequency of application, or substitute with a less potent corticosteroid.

The following trial evaluated the effects of WYNZORA Cream on HPA axis suppression:

HPA axis suppression was evaluated in adult subjects (N=27) with extensive psoriasis (including scalp). Adrenal suppression was seen in 6 out of 26 subjects (23%) after 4 weeks of treatment, and in 3 out of 25 subjects (12%) after 8 weeks of treatment [see *Clinical Pharmacology (12.2)*].

Cushing's Syndrome and Hyperglycemia

Cushing's syndrome and hyperglycemia may occur due to the systemic effects of the topical corticosteroid. These complications generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids.

Additional Considerations for Endocrine Adverse Reactions

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios [see *Use in Specific Populations (8.4)*].

Use of more than one corticosteroid-containing product at the same time may increase total systemic corticosteroid exposure.

5.3 Allergic Contact Dermatitis with Topical Corticosteroids

Allergic contact dermatitis to a topical corticosteroid is usually diagnosed by observing a failure to heal rather than a clinical exacerbation. Such an observation should be corroborated with appropriate diagnostic patch testing.

5.4 Allergic Contact Dermatitis with Topical Calcipotriene

Allergic contact dermatitis has been observed with use of topical calcipotriene. Such an observation should be corroborated with appropriate diagnostic patch testing.

5.5 Ophthalmic Adverse Reactions

Use of topical corticosteroids, including WYNZORA Cream, may increase the risks of glaucoma and posterior subcapsular cataract. Cataracts and glaucoma have been reported with the postmarketing use of topical corticosteroid products [see *Adverse Reactions (6.2)*].

Avoid contact of WYNZORA Cream with eyes. WYNZORA Cream may cause eye irritation. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The rates of adverse reactions given below were reported in a randomized, multicenter, prospective, vehicle and active controlled clinical trial in adult subjects with plaque psoriasis. Subjects applied WYNZORA Cream, calcipotriene/betamethasone dipropionate topical suspension, 0.005%/0.064% or vehicle once daily for 8 weeks. The mean weekly dose of WYNZORA Cream was 33.8 g. A total of 342 subjects were treated with WYNZORA Cream, 337 with calcipotriene/betamethasone dipropionate topical suspension, 0.005%/0.064% and 115 with vehicle. The majority of subjects were White (87%) and male (62%). Approximately 72% were non-Hispanic/Latino. The mean age was 52 years and ages ranged from 18 to 89 years.

The most common adverse reactions reported by $\geq 1\%$ of subjects treated with WYNZORA Cream and more frequently than vehicle are presented in Table 1 below.

Table 1: Adverse Reactions Through Week 8

Preferred Term	WYNZORA Cream (N=342)	Vehicle Cream (N=115)
Upper Respiratory Infection (URI) ^a	7%	5%
Headache	2%	0%
Application site irritation	1%	0%

^a Includes nasopharyngitis, upper respiratory tract infection (URTI), and viral URTI

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of topical corticosteroids. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing reports for local adverse reactions to topical corticosteroids included: atrophy, striae, telangiectasias, itching, dryness, hypopigmentation, perioral dermatitis, secondary infection, and miliaria.

Ophthalmic adverse reactions of cataracts, glaucoma, and increased intraocular pressure, have been reported during use of topical corticosteroids, including topical betamethasone products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with WYNZORA Cream are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes. Although there are no available data on use of the calcipotriene component in pregnant women, systemic exposure to calcipotriene after topical administration of WYNZORA Cream is likely to be low [see *Clinical Pharmacology* (12.3)].

Observational studies suggest an increased risk of having low birthweight infants with the maternal use of potent or very potent topical corticosteroids (see *Data*). Advise pregnant women that WYNZORA Cream may increase the potential risk of having a low birth weight infant and to use WYNZORA Cream on the smallest area of skin and for the shortest duration possible.

In animal reproduction studies, oral administration of calcipotriene to pregnant rats during the period of organogenesis resulted in an increased incidence of minor skeletal abnormalities, including

enlarged fontanelles and extra ribs (*see Data*). Oral administration of calcipotriene to pregnant rabbits during the period of organogenesis had no apparent effects on embryo-fetal development. Subcutaneous administration of betamethasone dipropionate to pregnant rats and rabbits during the period of organogenesis resulted in fetal toxicity, including fetal deaths, reduced fetal weight, and fetal malformations (cleft palate and crooked or short tail) (*see Data*). The available data do not allow the calculation of relevant comparisons between the systemic exposures of calcipotriene and betamethasone dipropionate observed in animal studies to the systemic exposures that would be expected in humans after topical use of WYNZORA Cream.

The background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency. However, when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data

Embryo-fetal development studies with calcipotriene were performed by the oral route in rats and rabbits. Pregnant rats received dosages of 0, 6, 18, or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m²/day, respectively) on days 6-15 of gestation (the period of organogenesis). There were no apparent effects on maternal survival, behavior, or body weight gain, no effects on litter parameters, and no effects on the incidence of major malformations in fetuses. Fetuses from dams dosed at 54 mcg/kg/day exhibited a significantly increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs.

Pregnant rabbits were dosed daily with calcipotriene at exposures of 0, 4, 12, or 36 mcg/kg/day (0, 48, 144, and 432 mcg/m²/day, respectively) on days 6-18 of gestation (the period of organogenesis). Mean maternal body weight gain was reduced in animals dosed at 12 or 36 mcg/kg/day. The incidence of fetal deaths was increased in the group dosed at 36 mcg/kg/day; reduced fetal weight was also observed in this group. The incidence of major malformations among fetuses was not affected. An increase in the incidence of minor skeletal abnormalities, including incomplete ossification of sternbrae, pubic bones, and forelimb phalanges, was observed in the group dosed at 36 mcg/kg/day.

Embryo-fetal development studies with betamethasone dipropionate were performed via subcutaneous injection in mice and rabbits. Pregnant mice were administered doses of 0, 156, 625, or 2500 mcg/kg/day (0, 468, 1875, and 7500 mcg/m²/day, respectively) on days 7 through 13 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, malformations (increased incidence of the cleft palate and crooked or short tail), and minor skeletal abnormalities (delayed ossification of vertebra and sternbrae). Fetal toxicity was observed at the lowest exposure that was evaluated (156 mcg/kg/day).

Pregnant rabbits were injected subcutaneously at dosages of 0, 0.625, 2.5, and 10 mcg/kg/day (0, 7.5, 30, and 120 mcg/m²/day, respectively) on days 6 through 18 of gestation (the period of

organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, external malformations (including malformed ears, cleft palate, umbilical hernia, kinked tail, club foot, and club hand), and skeletal malformations (including absence of phalanges of the first digit and cranial dysplasia) at dosages of 2.5 mcg/kg/day and above.

Calcipotriene was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 6, 18 or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m² /day, respectively) from gestation day 15 through day 20 postpartum. No remarkable effects were observed on any parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.

Betamethasone dipropionate was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 100, 300, and 1000 mcg/kg/day (0, 600, 1800, and 6000 mcg/m² /day, respectively) from gestation day 6 through day 20 postpartum. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/ kg/day. No effects on the ability of pups to learn were observed, and the ability of the offspring of treated rats to reproduce was not affected.

8.2 Lactation

Risk Summary

There is no information regarding the presence of topically administered calcipotriene and betamethasone dipropionate in human milk, the effects on the breastfed infant, or the effects on milk production. Concentrations of calcipotriene in plasma are low after topical administration, and therefore, concentrations in human milk are likely to be low [see *Clinical Pharmacology (12.3)*].

It is not known whether topically administered calcipotriene or corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WYNZORA Cream and any potential adverse effects on the breastfed child from WYNZORA Cream or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use WYNZORA Cream on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply WYNZORA Cream directly to the nipple and areola to avoid direct infant exposure.

8.4 Pediatric Use

Safety and effectiveness of the use of WYNZORA Cream in adolescents and pediatric patients under the age of 18 years have not been established.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity when treated with topical corticosteroids. Pediatric patients are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency with the use of topical corticosteroids including WYNZORA Cream [see *Clinical Pharmacology (12.2)*].

Systemic toxicities such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids. Local adverse reactions including striae have also been reported with use of topical corticosteroids in pediatric patients.

8.5 Geriatric Use

The trial included 66 subjects \geq 65 years of age treated with WYNZORA Cream.

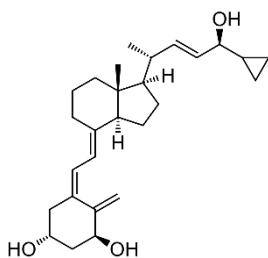
No overall differences in safety or effectiveness of WYNZORA Cream were observed between these subjects and younger subjects. All other reported clinical experience has not identified any differences in response between elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

WYNZORA (calcipotriene and betamethasone dipropionate) Cream contains anhydrous calcipotriene and betamethasone dipropionate intended for topical use.

Calcipotriene is a synthetic vitamin D3 analog.

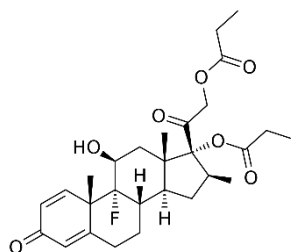
Chemically, calcipotriene is (5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22 tetraene-1 α ,3 β ,24-triol, with the empirical formula $C_{27}H_{40}O_3$, a molecular weight of 412.6, and the following structural formula:



Calcipotriene is a white or almost white powder. It is insoluble in water, freely soluble in ethanol and slightly soluble in methylene chloride.

Betamethasone dipropionate is a synthetic corticosteroid.

Betamethasone dipropionate has the chemical name Pregna-1,4-diene-3,20-dione,9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11 β , 16 β), with the empirical formula $C_{28}H_{37}FO_7$, a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to almost white crystalline powder. It is practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in alcohol.

Each gram of WYNZORA Cream contains 50 mcg of calcipotriene and 0.644 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone). WYNZORA Cream also contains the following inactive ingredients: isopropyl myristate, mineral oil, medium-chain triglycerides, isopropyl alcohol, polyoxyl lauryl ether, poloxamer (407), polyoxyl 40 hydrogenated castor oil, carbomer interpolymer (type A), butylated hydroxyanisole, trolamine, dibasic sodium phosphate, heptahydrate, monobasic sodium phosphate, monohydrate, alpha-tocopherol and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

WYNZORA Cream combines the pharmacological effects of calcipotriene as a synthetic vitamin D3 analog and betamethasone dipropionate as a synthetic corticosteroid. However, while their pharmacologic and clinical effects are known, the exact mechanisms of their actions in plaque psoriasis are unknown.

12.2 Pharmacodynamics

Vasoconstriction:

In a vasoconstrictor trial in healthy subjects, the skin blanching response of WYNZORA Cream was consistent with a mid-strength corticosteroid when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression:

HPA axis suppression was evaluated in adult subjects with extensive psoriasis involving 20-30% of the body surface area (including scalp). Treatment consisted of once daily application of WYNZORA Cream to the body (including scalp involvement in 75% of the subjects) for up to 8 weeks. Adrenal suppression indicated by 30-minute post-stimulation serum cortisol level of ≤ 18 mcg/dL was seen in 6 out of 26 subjects (23%) after 4 weeks of treatment, and in 3 out of 25 subjects (12%; one subject with continued suppression from Week 4 and two additional subjects) after 8 weeks of treatment.

There was no trend towards decreasing cortisol levels post-ACTH stimulation with increasing systemic concentration of betamethasone 17-propionate (B17P) measured as AUC_{0-7} or C_{max} or increasing average weekly amount of WYNZORA Cream used.

Effects on Calcium Metabolism:

The effects on calcium metabolism of once daily application of WYNZORA Cream to the body (including scalp involvement in 75% of subjects) for up to 8 weeks were also examined and no cases of hypercalcemia and no clinically relevant changes in urine calcium were reported.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of WYNZORA Cream was investigated in adult subjects in the same study as described above [see *Clinical Pharmacology (12.2)*]. Their mean \pm SD total body surface area involvement was 25 ± 5 % and 74% of the subjects presented with scalp involvement and with a

mean \pm SD scalp involvement of 52 ± 40 %. The mean \pm SD weekly dose during the 8 weeks of treatment was 79 ± 30 g.

Plasma concentrations of calcipotriene and betamethasone dipropionate and their major metabolites were measured after 4 weeks and 8 weeks of once daily application of WYNZORA Cream.

In most samples, concentrations of the four analytes were below or close to lower limit of quantification (LOQ). One of 27 (4%) subjects had quantifiable levels of calcipotriene at Week 4 and the C_{\max} and AUC_{0-7} were 30 pg/mL and 229 pg*h/mL, respectively. For the major metabolite of calcipotriene, MC1080, 3 of 27 (11%) subjects had quantifiable levels at Week 4. The mean \pm SD C_{\max} and AUC_{0-7} were 30 ± 4 pg/mL and 224 ± 16 pg*h/mL, respectively. No subjects had quantifiable levels of calcipotriene or MC1080 at Week 8.

There were 3 of 27 subjects (11%) with quantifiable levels of betamethasone dipropionate at Week 4. The mean \pm SD of C_{\max} and AUC_{0-7} were 22 ± 9 pg/mL and 160 ± 36 pg*h/mL, respectively. The major metabolite of betamethasone dipropionate, B17P, was quantifiable in 13 of 27 subjects (48%) at Week 4. The mean \pm SD C_{\max} and AUC_{0-7} were 96 ± 234 pg/mL and 419 ± 646 pg*h/mL, respectively. No subjects had quantifiable levels of betamethasone dipropionate at Week 8, whereas 7 of 19 (37%) subjects had quantifiable levels of B17P. The mean \pm SD C_{\max} and AUC_{0-7} were 31 ± 29 pg/mL and 205 ± 142 pg*h/mL, respectively.

Metabolism

Calcipotriene:

Calcipotriene metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriene are less potent than the parent compound.

Calcipotriene is metabolized to MC1046 (the α,β -unsaturated ketone analog of calcipotriene), which is metabolized further to MC1080 (a saturated ketone analog). MC1080 is the major metabolite in plasma. MC1080 is slowly metabolized to calcitroic acid.

Betamethasone dipropionate:

Betamethasone dipropionate is metabolized by hydrolysis to betamethasone 17-propionate and betamethasone, including the 6β -hydroxy derivatives of those compounds. Betamethasone 17-propionate (B17P) is the primary metabolite.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10, and 30 mcg/kg/day (corresponding to 9, 30, and 90 mcg/m²/day), no significant changes in tumor incidence were observed when compared to control.

A 104-week oral carcinogenicity study was conducted with calcipotriene in male and female rats at doses of 1, 5 and 15 mcg/kg/day (corresponding to dosages of approximately 6, 30, and 90 mcg/m²/day). Beginning week 71, the dosage for high-dose animals of both genders was reduced to 10 mcg/kg/day (corresponding to a dosage of approximately 60 mcg/m²/day). A treatment-related increase in benign C-cell adenomas was observed in the thyroid of females that received 15 mcg/kg/day. A treatment-related increase in benign pheochromocytomas was observed in the adrenal glands of males that received 15 mcg/kg/day. No other statistically significant differences in tumor

incidence were observed when compared to control. The relevance of these findings to patients is unknown.

When betamethasone dipropionate was applied topically to CD-1 mice for up to 24 months at dosages approximating 1.3, 4.2, and 8.5 mcg/kg/day in females, and 1.3, 4.2, and 12.9 mcg/kg/day in males (corresponding to dosages of up to approximately 26 mcg/m²/day and 39 mcg/m²/day, in females and males, respectively), no significant changes in tumor incidence were observed when compared to control.

When betamethasone dipropionate was administered via oral gavage to male and female Sprague Dawley rats for up to 24 months at dosages of 20, 60, and 200 mcg/kg/day (corresponding to dosages of approximately 120, 360, and 1200 mcg/m²/day), no significant changes in tumor incidence were observed when compared to control.

Calcipotriene did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

Studies in rats with oral doses of up to 54 mcg/kg/day (324 mcg/m²/day) of calcipotriene indicated no impairment of fertility or general reproductive performance. Studies in male rats at oral doses of up to 200 mcg/kg/day (1200 mcg/m²/day), and in female rats at oral doses of up to 1000 mcg/kg/day (6000 mcg/m²/day), of betamethasone dipropionate indicated no impairment of fertility.

14 CLINICAL STUDIES

The safety and efficacy of WYNZORA Cream were evaluated in a randomized, multicenter, vehicle and active-comparator controlled, clinical trial (NCT03308799) in adult subjects with mild to moderate plaque psoriasis. In the trial, 794 subjects were randomized to 1 of 3 treatment groups: WYNZORA Cream, vehicle cream, or calcipotriene/betamethasone dipropionate topical suspension, 0.005%/0.064%. The majority of subjects in the trial (81.7%) had disease of moderate severity at baseline, while 18.3% of subjects had disease of mild severity. Disease severity was determined by a 5-grade Physician's Global Assessment (PGA) scale.

The primary efficacy endpoint was the proportion of subjects with treatment success at Week 8. Treatment success was defined as at least a 2-grade improvement from baseline in the PGA score and an PGA score equating to "clear" or "almost clear". Other evaluated outcomes included reduction in itch as defined by at least a 4-point improvement in the 11-point peak pruritus numeric rating scale (NRS) from baseline to Week 4. Table 2 presents the primary efficacy results.

Table 2: Primary Efficacy Outcome at Week 8

	WYNZORA Cream (N=342)	Vehicle Cream (N=115)
PGA of Clear or Almost Clear And ≥2-grade Improvement	37.4%	3.7%
Difference from Vehicle (95% CI)	33.7% (27.4%, 40.0%)	

WYNZORA Cream was non-inferior to calcipotriene/betamethasone dipropionate topical suspension, 0.005%/0.064% for the primary endpoint of treatment success at Week 8 [Difference (95% CI): 14.6% (7.6%, 21.6%)].

Among subjects who had at least a peak pruritus NRS score of 4 at baseline, there was a higher percentage of subjects that achieved at least a 4-point improvement from baseline on the peak pruritus NRS score at Week 4 in the WYNZORA Cream group compared to the vehicle cream group (60.3% vs. 21.4%).

16 HOW SUPPLIED/STORAGE AND HANDLING

WYNZORA® (calcipotriene and betamethasone dipropionate) Cream, 0.005%/0.064%, is a white cream. Each gram of cream contains 50 mcg of anhydrous calcipotriene and 0.644 mg of betamethasone dipropionate. It is available as 60 g tubes individually packaged (NDC 73499-001-01).

Store between 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F). [See USP controlled room temperature.]

Do not freeze. Protect from light and excessive heat.

Unused product should be discarded six months after the tube has been opened.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Administration Instructions

- Instruct patients not to use more than 100 grams per week.
- Instruct patients to discontinue therapy when control is achieved unless directed otherwise by the healthcare provider.
- Advise patients to avoid use of WYNZORA Cream on the face, underarms, groin or eyes.
- Advise patients not to occlude the treatment area with a bandage or other covering unless directed by the healthcare provider.
- Instruct patients to wash hands after application.

Local Reactions and Skin Atrophy

Advise patients that local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids.

Hypercalcemia and Hypercalciuria

Advise patients that hypercalcemia and hypercalciuria may occur with the use of WYNZORA Cream [see *Warnings and Precautions* (5.1)].

HPA Axis Suppression, Cushing's Syndrome, and Hyperglycemia

Advise patients that WYNZORA Cream can cause HPA axis suppression, Cushing's syndrome, and/or hyperglycemia [see *Warnings and Precautions* (5.2)].

Ophthalmic Adverse Reactions

Advise patients to avoid contact of WYNZORA Cream with eyes and to report any visual symptoms [see *Warnings and Precautions* (5.5)].

Possible Avoidance of Other Products Containing Calcipotriene or a Corticosteroid

Instruct patients not to use other products containing calcipotriene or a corticosteroid with WYNZORA Cream without first talking to the healthcare provider.

Pregnancy and Lactation

- Advise pregnant women that WYNZORA Cream may increase the potential risk of having a low birth weight infant and to use WYNZORA Cream on the smallest area of skin and for the shortest duration possible [*see Use in Specific Populations (8.1)*].
- Advise breastfeeding women not to apply WYNZORA Cream directly to the nipple and areola to avoid direct infant exposure [*see Use in Specific Populations (8.2)*].

Manufactured for:

MC2 Therapeutics, Ltd. Leatherhead, KT22 7EP, United Kingdom

Distributed by:

EPI Health, LLC. Charleston, SC 29403, USA