

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SERNIVO™ Spray safely and effectively. See full prescribing information for SERNIVO™ Spray.

SERNIVO™ (betamethasone dipropionate) Spray, 0.05% for topical use
Initial U.S. Approval: 1975

INDICATIONS AND USAGE

SERNIVO Spray is a corticosteroid indicated for the treatment of mild to moderate plaque psoriasis in patients 18 years of age or older. (1)

DOSAGE AND ADMINISTRATION

- Apply to the affected skin areas twice daily. Rub in gently. (2)
- Use SERNIVO Spray for up to 4 weeks and not beyond. (2)
- Discontinue treatment when control is achieved. (2)
- Do not use if atrophy is present at the treatment site. (2)
- Do not use with occlusive dressings unless directed by a physician. (2)
- Avoid use on the face, scalp, axilla, groin, or other intertriginous areas. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Spray: 0.05% (equivalent to 0.5 mg betamethasone/g) (3)

CONTRAINDICATIONS

- None. (4)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SERNIVO Spray is indicated for the treatment of mild to moderate plaque psoriasis in patients 18 years of age or older.

2 DOSAGE AND ADMINISTRATION

Shake well before use.

Apply SERNIVO Spray to the affected skin areas twice daily and rub in gently.

Use SERNIVO Spray for up to 4 weeks of treatment. Treatment beyond 4 weeks is not recommended.

Discontinue SERNIVO Spray when control is achieved.

Do not use if atrophy is present at the treatment site.

Do not bandage, cover, or wrap the treated skin area unless directed by a physician. Avoid use on the face, scalp, axilla, groin, or other intertriginous areas.

SERNIVO Spray is for topical use only. It is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Spray, 0.05% for topical use. Each gram of SERNIVO Spray contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a slightly thickened, white to off-white oil-in-water emulsion.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression and Other Unwanted Systemic Glucocorticoid Effects

SERNIVO Spray can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during or after withdrawal of treatment. Factors that predispose to HPA axis suppression include the use of high-potency corticosteroids, 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.

In a study including 48 evaluable subjects 18 years of age or older with moderate to severe plaque psoriasis, abnormal ACTH stimulation test results suggestive of adrenal suppression were identified in 5 out of 24 (20.8%) subjects after treatment with SERNIVO Spray twice daily for 15 days. No subject (0 out of 24) had abnormal ACTH stimulation test results after treatment with SERNIVO Spray twice daily for 29 days [see *Clinical Pharmacology* (12.2)].

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. If signs and symptoms of steroid withdrawal occur, supplemental systemic corticosteroids may be required.

Systemic effects of topical corticosteroids may also manifest as Cushing's syndrome, hyperglycemia, and glucosuria. These events are rare and generally occur after prolonged exposure to larger than recommended doses, particularly with high-potency topical corticosteroids.

Minimize the unwanted risks from endocrine effects by mitigating the risk factors favoring increased systemic bioavailability and by using the product as recommended [see *Dosage and Administration* (2)].

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. Use of SERNIVO Spray is not recommended in pediatric patients [see *Use in Specific Populations* (8.4)].

5.2 Allergic Contact Dermatitis

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Corroborate such an observation with appropriate diagnostic patch testing. If irritation develops, discontinue the topical corticosteroid and institute appropriate therapy.

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 clinical practice.

WARNINGS AND PRECAUTIONS

- SERNIVO Spray can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency during or after treatment. (5.1)
- Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can result from systemic absorption of topical corticosteroids. (5.1)
- Use of topical corticosteroids may require periodic evaluation for HPA axis suppression. (5.1)
- Modify use if HPA axis suppression develops. (5.1)
- High potency corticosteroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure and young age may predispose patients to HPA axis suppression. (5.1)
- Pediatric patients may be more susceptible to systemic toxicity when treated with topical corticosteroids. (5.1, 8.4)

ADVERSE REACTIONS

The most common adverse reactions (≥1%) are application site reactions, including pruritus, burning and/or stinging, pain, and atrophy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Promius Pharma, LLC, at 1-888-966-8766 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

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

In two randomized, multicenter, prospective vehicle-controlled clinical trials, subjects with moderate plaque psoriasis of the body applied SERNIVO Spray or vehicle spray twice daily for 4 weeks. A total of 352 subjects applied SERNIVO Spray and 180 subjects applied vehicle spray.

Adverse reactions that occurred in at least 1% of subjects treated with SERNIVO Spray for up to 28 days are presented in Table 1.

Table 1: Adverse Reactions Occurring in ≥1% of Subjects Treated with SERNIVO Spray for up to Four Weeks

| | SERNIVO Spray <i>b.i.d.</i> (N=352) | Vehicle Spray <i>b.i.d.</i> (N=180) |
|--|--|--|
| Application site pruritus | 6.0% | 9.4% |
| Application site burning and/or stinging | 4.5% | 10.0% |
| Application site pain | 2.3% | 3.9% |
| Application site atrophy | 1.1% | 1.7% |

Less common adverse reactions (with occurrence lower than 1% but higher than 0.1%) in subjects treated with SERNIVO spray were application site reactions including telangiectasia, dermatitis, discoloration, folliculitis and skin rash, in addition to dysgeusia and hyperglycemia. These adverse reactions were not observed in subjects treated with vehicle.

6.2 Postmarketing Experience

Because adverse 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 have also included striae, irritation, dryness, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, hypertrichosis, and miliaria.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. SERNIVO Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. The abnormalities observed included umbilical hernias, cephalocele, and cleft palate.

8.3 Nursing Mothers

Systemically administered corticosteroids appear in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids can result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when SERNIVO Spray is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of SERNIVO Spray in patients younger than 18 years of age have not been studied; therefore use in pediatric patients is not recommended. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk of systemic toxicity, including HPA axis suppression and adrenal insufficiency, when treated with topical drugs. [see *Warnings and Precautions* (5.1)]

Rare systemic effects 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 skin atrophy have also been reported with use of topical corticosteroids in pediatric patients.

8.5 Geriatric Use

Clinical studies of SERNIVO Spray did not include sufficient numbers of subjects who were 65 years of age or older to determine whether they respond differently from younger subjects.

PATIENT INFORMATION

SERNIVO™ (ser-ne-vo) (betamethasone dipropionate) Spray, 0.05%

Important: SERNIVO Spray is for use on the skin only. Do not get SERNIVO Spray near or in your eyes, mouth, or vagina.

What is SERNIVO Spray?

- SERNIVO Spray is a prescription corticosteroid medicine used to treat mild to moderate plaque psoriasis in people 18 years of age and older.

It is not known if SERNIVO Spray is safe and effective in children under 18 years of age. SERNIVO Spray is not recommended for use in patients under 18 years of age.

Before you use SERNIVO Spray, tell your doctor about all of your medical conditions, including if you:

- are allergic to any of the ingredients in SERNIVO Spray. See the end of this leaflet for a list of the ingredients in SERNIVO Spray.
- have thinning of the skin (atrophy) at the treatment site
- are pregnant or plan to become pregnant. It is not known if SERNIVO Spray will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SERNIVO Spray passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take other corticosteroid medicines by mouth or use other products on your skin that contain corticosteroids.

How should I use SERNIVO Spray?

See the “Instructions for Use” for detailed information about the right way to apply SERNIVO Spray.

- Use SERNIVO Spray exactly as your doctor tells you to use it.
- Your doctor should tell you how much SERNIVO Spray to use and where to apply it.
- Apply SERNIVO Spray 2 times a day.
- Use SERNIVO Spray for the shortest amount of time needed to treat your plaque psoriasis. Tell your doctor if your skin condition is not getting better after 4 weeks of using SERNIVO Spray. Do not use SERNIVO Spray for longer than 4 weeks.
- Wash hands after applying SERNIVO Spray.
- Do not use SERNIVO Spray on your face, scalp, underarms (armpits), groin, or areas where your skin may touch or rub together.
- Do not bandage, cover, or wrap the treated skin area, unless your doctor tells you to.

What are the possible side effects of SERNIVO Spray?

- SERNIVO Spray can pass through your skin.** Too much SERNIVO Spray passing through your skin can cause your adrenal glands to stop working. Your doctor may do blood tests to check for adrenal gland problems.

The most common side effects of SERNIVO Spray include itching, burning, stinging, pain, and thinning of skin (atrophy) at the treated site.

These are not all the possible side effects of SERNIVO Spray.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SERNIVO Spray?

- Store SERNIVO Spray at room temperature between 68°F to 77°F (20°C to 25°C).
- Throw away (discard) any unused SERNIVO Spray after 4 weeks.

Keep SERNIVO Spray and all medicines out of the reach of children.

General information about the safe and effective use of SERNIVO Spray.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SERNIVO Spray for a condition for which it was not prescribed. Do not give SERNIVO Spray to other people even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about SERNIVO Spray that is written for health professionals.

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Spray, 0.05%
(betamethasone dipropionate)
(ser-ne-vo)
SERNIVO™

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PRESCRIBING INFORMATION

SERNIVO™ (ser-ne-vo)
(betamethasone dipropionate)
Spray, 0.05%



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What are the ingredients in SERNIVO Spray?

Active ingredient: betamethasone dipropionate

Inactive ingredients: butylated hydroxytoluene, cetostearyl alcohol, hydroxyethyl cellulose, methylparaben, mineral oil, oleyl alcohol, polyoxyl 20 cetostearyl ether, propylparaben, purified water, and sorbitan monostearate

Manufactured by: DPT Laboratories, Ltd., San Antonio, TX 78215

Distributed by: Promius Pharma, LLC., Princeton, NJ 08540

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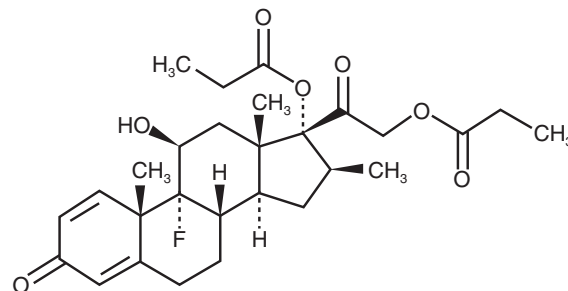
This Patient Information has been approved by the U.S. Food and Drug Administration

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11 DESCRIPTION

SERNIVO Spray contains 0.0643% betamethasone dipropionate (equivalent to 0.05% betamethasone), a synthetic, fluorinated corticosteroid.

The chemical name for betamethasone dipropionate is 9-fluoro-11(β), 17, 21-trihydroxy-16(β)-methylpregna-1,4-diene-3,20-dione-17,21-dipropionate. The empirical formula is C₂₈H₃₇F₂O₇, and the molecular weight is 504.6. The structural formula is shown below.



Each gram of SERNIVO Spray contains 0.643 mg of betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a slightly thickened, white to off-white, oil-in-water, non-sterile emulsion with the following inactive ingredients: butylated hydroxytoluene, cetostearyl alcohol, hydroxyethyl cellulose, methylparaben, mineral oil, oleyl alcohol, polyoxyl 20 cetostearyl ether, propylparaben, purified water, and sorbitan monostearate. SERNIVO Spray is co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing to patients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action of SERNIVO Spray in psoriasis is unknown.

12.2 Pharmacodynamics

Vasoconstrictor studies performed with SERNIVO Spray in healthy subjects indicate that it is in the mid-range of potency as compared with other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.

The potential for HPA axis suppression by SERNIVO Spray was evaluated in a study randomizing 52 adult subjects with moderate to severe plaque psoriasis. SERNIVO Spray was applied twice daily for 15 or 29 days, in subjects with psoriasis involving a mean of 29.0% and 26.5% body surface area at baseline across the 2 treatment duration arms, respectively. Forty-eight (48) subjects were evaluated for HPA axis suppression at the end of treatment. The proportion of subjects demonstrating HPA axis suppression was 20.8% (5 out of 24) in subjects treated with SERNIVO Spray for 15 days. No subjects (0 out of 24) treated with SERNIVO Spray for 29 days had HPA axis suppression. In this study HPA axis suppression was defined as serum cortisol level ≤18 mcg/dL 30-minutes post-cosyntropin stimulation. In the 4 subjects with available follow-up values, all subjects had normal ACTH stimulation tests at follow-up.

12.3 Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids are absorbed through normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Plasma concentrations of betamethasone dipropionate, betamethasone-17-propionate, and betamethasone were measured at baseline, and before and after the last dose (1, 3, and 6 hours) in the HPA axis suppression trial in subjects with psoriasis [see *Clinical Pharmacology* (12.2)]. The majority of subjects had no measurable plasma concentration (<5.00 pg/mL) of betamethasone dipropionate, while the metabolites, betamethasone-17-propionate and betamethasone, were detected in the majority of subjects (Table 2). There was high variability in the data but there was a trend toward higher systemic exposure at Day 15 and lower systemic exposure at Day 29.

Table 2: Mean (±SD) Maximum Plasma Concentrations (pg/mL) of Betamethasone Dipropionate Metabolites after 15 or 29 Days of Treatment with SERNIVO Spray

| Analyte (pg/mL) | SERNIVO Spray <i>b.i.d.</i> (15 days) | SERNIVO Spray <i>b.i.d.</i> (29 days) |
|-----------------------------|---|---|
| Betamethasone-17-propionate | 120 ± 127 | 63.9 ± 52.6 |
| Betamethasone | 119 ± 176 | 57.6 ± 55.9 |

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of betamethasone dipropionate.

In a 90-day repeat-dose toxicity study in rats, topical administration of betamethasone dipropionate spray formulation at dose concentrations of 0.05% and 0.1% (providing dose levels up to 0.5 mg/kg/day in males and 0.25 mg/kg/day in females) resulted in a toxicity profile consistent with long-term exposure to corticosteroids including reduced body weight gain, adrenal atrophy, and histological changes in bone marrow, thymus and spleen indicative of severe immune suppression. A no observable adverse effect level (NOAEL) could not be determined in this study. Although the clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay.

Studies in rabbits, mice, and rats using intramuscular doses up to 1, 33, and 2 mg/kg, respectively, resulted in dose-related increases in fetal resorptions in rabbits and mice.

14 CLINICAL STUDIES

Two multi-center, randomized, double-blind, vehicle-controlled clinical trials were conducted in subjects aged 18 years and older with moderate plaque psoriasis. In both trials, randomized subjects applied SERNIVO Spray or vehicle spray to the affected areas twice daily for 28 days. Enrolled subjects had body surface area of involvement between 10% to 20%, and an Investigator Global Assessment (IGA) score of 3 (moderate).

Efficacy was assessed as the proportion of subjects who were considered a treatment success (defined as having an IGA score of 0 or 1 [clear or almost clear] and at least a 2-grade reduction from baseline). Table 3 presents the efficacy results at Day 15 and Day 29.

Table 3: Proportion of Subjects with Plaque Psoriasis with Treatment Success^a after 14 Days and 28 Days of Treatment

| | Study 1 | | Study 2 | |
|-----------------------------|---|--|---|--|
| | SERNIVO Spray <i>b.i.d.</i> (N=182) | Vehicle Spray <i>b.i.d.</i> (N=95) | SERNIVO Spray <i>b.i.d.</i> (N=174) | Vehicle Spray <i>b.i.d.</i> (N=87) |
| Treatment Success at Day 15 | 21.5% | 7.4% | 19.0% | 2.3% |
| Treatment Success at Day 29 | 42.7% | 11.7% | 34.5% | 13.6% |

^a Treatment success is defined as an IGA of 0 or 1 (clear or almost clear) and at least a 2-grade reduction from baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage

SERNIVO Spray is a slightly thickened, white to off-white, non-sterile emulsion supplied in high density polyethylene bottles with a heat induction seal lined polypropylene cap. The drug is supplied in the following volumes:

- 60 mL (NDC 67857-808-17)
- 120 mL (NDC 67857-808-04)

Store at controlled room temperature of 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See *USP Controlled Room Temperature*].

Each unit is co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing.

16.2 Handling/Instructions for the Pharmacist

1. Remove the spray pump from the wrapper.
2. Remove and discard the cap from the bottle.
3. Keeping the bottle upright, insert the spray pump into the bottle and turn clockwise until it is closed tightly.
4. Dispense the bottle with the spray pump inserted.
5. Include the date dispensed in the space provided on the carton.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Inform patients of the following:

- Discontinue therapy when control is achieved, unless directed otherwise by the physician.
- Do not use for longer than 4 consecutive weeks.
- Avoid contact with the eyes.
- Avoid use of SERNIVO Spray on the face, scalp, underarms, groin or other intertriginous areas, unless directed by the physician.
- Do not occlude the treatment area with bandage or other covering, unless directed by the physician.
- Local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use, or use of higher potency corticosteroids.

Manufactured by: DPT Laboratories, Ltd., San Antonio, TX 78215

Distributed by: Promius Pharma, LLC., Princeton, NJ 08540

Sernivo is a trademark of Promius Pharma, LLC.

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