CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

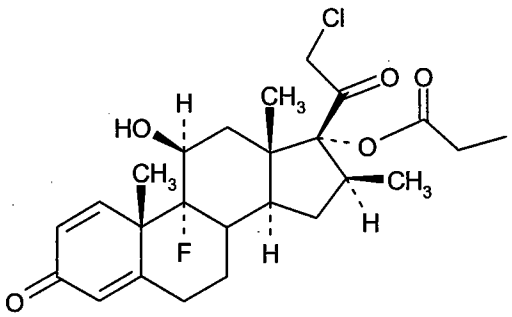
21-835

LABELING

CLOBEX® (clobetasol propionate) Spray, 0.05%
Rx only
For topical use only
Not for ophthalmic, oral or intravaginal use

DESCRIPTION: CLOBEX® (clobetasol propionate) Spray, 0.05% contains clobetasol propionate, a synthetic fluorinated corticosteroid, for topical use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Clobetasol propionate is 21-chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate, with the empirical formula $C_{25}H_{32}ClFO_5$, and a molecular weight of 466.97 (CAS Registry Number 25122-46-7).

The following is the chemical structure:



Clobetasol propionate is a white to almost white crystalline powder that is practically insoluble in water. Each gram of CLOBEX® (clobetasol propionate) Spray, 0.05% contains 0.5 mg of clobetasol propionate, in a vehicle base composed of alcohol, isopropyl myristate, sodium lauryl sulfate, and undecylenic acid.

CLINICAL PHARMACOLOGY: Like other topical corticosteroids CLOBEX® (clobetasol propionate) Spray, 0.05% has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier and occlusion. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and other disease processes in the skin may increase percutaneous absorption.

There are no human data regarding the distribution of corticosteroids to body organs following topical application. Nevertheless, once absorbed through the skin, topical corticosteroids are handled through metabolic pathways similar to systematically administered corticosteroids. They are metabolized,

primarily in the liver, and are then excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

CLOBEX® (clobetasol propionate) Spray, 0.05% is in the super-high range of potency as compared with other topical corticosteroids in a vasoconstrictor study conducted in healthy subjects. However, similar blanching scores do not necessarily imply therapeutic equivalence.

The effect of CLOBEX® (clobetasol propionate) Spray, 0.05% on hypothalamic-pituitary-adrenal (HPA) axis function was investigated in adults in two studies. In the first study, patients with plaque psoriasis covering at least 20% of their body applied CLOBEX® (clobetasol propionate) Spray, 0.05% twice daily for up to 4 weeks. Fifteen percent (2 out of 13) of patients displayed adrenal suppression after 4 weeks of use based on the Cosyntropin Stimulation Test. The laboratory suppression was transient; all subjects returned to normal after cessation of drug use. In the second study, patients with plaque psoriasis covering at least 20% of their body applied CLOBEX® (clobetasol propionate) Spray, 0.05% twice daily for either 2 or 4 weeks. Nineteen percent (4 out of 21) of patients treated for 2 weeks and 20% (3 out of 15) of patients treated for 4 weeks displayed adrenal suppression at the end of treatment based on the Cosyntropin Stimulation Test. The laboratory suppression was transient; all subjects returned to normal after cessation of drug use. In these studies, HPA axis suppression was defined as serum cortisol level $\leq$ 18 µg/dL 30-min post cosyntropin ($ACTH_{1-24}$) stimulation (see PRECAUTIONS).

CLINICAL STUDIES: The efficacy of CLOBEX® (clobetasol propionate) Spray, 0.05% in psoriasis has been demonstrated in two randomized, vehicle controlled clinical trials, which were identical in design. The studies were conducted in patients aged 18 years and older with moderate to severe plaque psoriasis. Patients were treated twice daily for up to 4 weeks with either CLOBEX® (clobetasol propionate) Spray, 0.05% or vehicle spray.

Patients were evaluated on their Overall Disease Severity, a 5-point scale based on scaling, erythema, and plaque elevation that classified subjects as clear, almost clear, mild, moderate, or severe/very severe. Only patients classified as moderate or severe/very severe at baseline were enrolled in the studies. The median percent body surface area (BSA) at baseline was 6% for the two studies. The numbers of patients scored as clear or almost clear at Weeks 2 and 4 are presented in Table 1.

Table 1 – Number of Patients Clear or Almost Clear on the Overall Disease Severity Scale at Weeks 2 and 4

		Study 1		Study 2	
		CLOBEX N=60	Vehicle N=60	CLOBEX N=60	Vehicle N=60
Week 2	Clear	1 (2%)	0 (0%)	0 (0%)	0 (0%)
	Almost Clear	32 (53%)	1 (2%)	28 (47%)	0 (0%)
Week 4	Clear	15 (25%)	0 (0%)	18 (30%)	0 (0%)
	Almost Clear	32 (53%)	2 (3%)	31 (52%)	1 (2%)

INDICATIONS AND USAGE: CLOBEX® (clobetasol propionate) Spray, 0.05% is a super-high potent topical corticosteroid formulation indicated for the treatment of moderate to severe plaque psoriasis affecting up to 20% body surface area (BSA) in patients 18 years of age or older (see

PRECAUTIONS). Treatment should be limited to 4 consecutive weeks. The total dosage should not exceed 50 g (59 mL or 2 fl. oz.) per week.

Before prescribing for more than 2 weeks, any additional benefits of extending treatment to 4 weeks should be weighed against the risk of HPA axis suppression.

Patients should be instructed to use CLOBEX® (clobetasol propionate) Spray, 0.05% for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS).

Use in patients under 18 years of age is not recommended because safety has not been established and because numerically high rates of HPA axis supression were seen with other clobetasol propionate topical formulations. (see PRECAUTIONS: Pediatric Use).

CONTRAINDICATIONS: CLOBEX® (clobetasol propionate) Spray, 0.05% is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS:
General: Clobetasol propionate is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at the lowest doses tested.

In studies evaluating the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression, using the Cosyntropin Stimulation Test, CLOBEX® (clobetasol propionate) Spray, 0.05% demonstrated rates of suppression that were comparable after 2 and 4 weeks of twice-daily use (19% and 15-20%, respectively), in adult patients with moderate to severe plaque psoriasis (≥20%BSA). In these studies, HPA axis suppression was defined as serum cortisol level ≤ 18 μg/dL 30-min post cosyntropin stimulation (see CLINICAL PHARMACOLOGY).

Patients with acute illness or injury may have increased morbidity and mortality with intermittent HPA axis suppression. Patients should be instructed to use CLOBEX® (clobetasol propionate) Spray, 0.05% for the minimum amount of time necessary to achieve the desired results (see INDICATIONS AND USAGE).

Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

HPA axis suppression has not been evaluated in psoriasis patients treated with Clobex® Spray who are less than 18 years old. Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use). The potential increase in systemic exposure does not correlate with any proven benefit, but may lead to an increased potential for hypothalamic-pituitary-adrenal (HPA) axis supression.

Conditions which increase systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of adrenal suppression (see laboratory tests below). If adrenal suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to

substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids.
For information on systemic supplementation, see prescribing information for those products.

If irritation develops, CLOBEX® (clobetasol propionate) Spray, 0.05% should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation, as with most topical products not containing corticosteroids.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, use of CLOBEX® (clobetasol propionate) Spray, 0.05% should be discontinued until the infection has been adequately controlled.

CLOBEX® (clobetasol propionate) Spray, 0.05% should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face, groin, or axillae.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician and should not be used longer than the prescribed time period.
- This medication should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged, otherwise covered, or wrapped so as to be occlusive unless directed by the physician.
- Patients should wash their hands after applying the medication.
- Patients should report any signs of local or systemic adverse reactions to the physician.
- Patients should inform their physicians that they are using CLOBEX® (clobetasol propionate) Spray, 0.05% if surgery is contemplated.
- This medication is for external use only. It should not be used on the face, underarms, or groin area. Also avoid contact with the eyes and lips.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.
- Patients should not use more than 50 g (59 mL or 2 fl. oz.) per week of CLOBEX® (clobetasol propionate) Spray, 0.05%.

Instructions to the Pharmacist:

1. Remove the spray pump from the wrapper
2. Remove and discard the cap from the bottle
3. Keeping the bottle vertical, insert the spray pump into the bottle and turn clockwise until well-fastened
4. Dispense the bottle with the spray pump inserted

Laboratory Tests: The Cosyntropin Stimulation Test may be helpful in evaluating patients for HPA axis suppression.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Clobetasol propionate was negative in the *in vitro* mammalian chromosomal aberration test and in the *in vivo* mammalian erythrocyte micronucleus test.

The effect of subcutaneously administered clobetasol propionate on fertility and general reproductive toxicity was studied in rats at doses of 0, 12.5, 25, and 50 µg/kg/day. Males were treated beginning 70 days before mating and females beginning 15 days before mating through day 7 of gestation. A dosage level of less than 12.5 µg/kg/day clobetasol propionate was considered to be the no-observed-effect-level (NOEL) for paternal and maternal general toxicity based on decreased weight gain and for male reproductive toxicity based on increased weights of the seminal vesicles with fluid. The female reproductive NOEL was 12.5 µg/kg/day (ratio of animal dose to proposed human dose of 0.03 on a mg/m^2/day basis) based on reduction in the numbers of estrous cycles during the pre-cohabitation period and an increase in the number of nonviable embryos at higher doses.

Pregnancy: *Teratogenic effects:* Pregnancy Category C.
Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

The effect of clobetasol propionate on pregnancy outcome and development of offspring was studied in the rat.

Clobetasol propionate was administered subcutaneously to female rats twice daily (0, 12.5, 25, and 50 µg/kg/day) from day 7 of presumed gestation through day 25 of lactation or day 24 presumed gestation for those rats that did not deliver a litter. The maternal NOEL for clobetasol propionate was less than 12.5 µg/kg/day due to reduced body weight gain and feed consumption during the gestation period. The reproductive NOEL in the dams was 25 µg/kg/day (ratio of animal dose to proposed human dose of 0.07 on a mg/m^2/day basis) based on prolonged delivery at a higher dose level. The no-observed-adverse-effect-level (NOAEL) for viability and growth in the offspring was 12.5 µg/kg/day (ratio of animal dose to proposed human dose of 0.03 on a mg/m^2/day basis) based on incidence of stillbirths, reductions in pup body weights on days 1 and 7 of lactation, increased pup mortality, increases in the incidence of umbilical hernia, and increases in the incidence of pups with cysts on the kidney at higher dose levels during the preweaning period. The weights of the epididymides and testes were significantly reduced at higher dosages. Despite these changes, there were no effects on the mating and fertility of the offspring.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. CLOBEX® (clobetasol propionate) Spray, 0.05% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when CLOBEX® (clobetasol propionate) Spray, 0.05% is administered to a nursing woman.

Pediatric Use: Use in patients under 18 years of age is not recommended Use in patients under 18 years of age is not recommended, because safety has not been established and because numerically high rates of HPA axis suppression were seen with other clobetasol propionate topical formulations. Safety and effectiveness in pediatric patients treated with Clobex® Spray have not been established (established (see PRECAUTIONS: General).

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use: Clinical studies of CLOBEX® (clobetasol propionate) Spray, 0.05% did not include sufficient numbers of patients aged 65 and over to adequately determine whether they respond differently than younger patients. In the two Phase 3 studies, 21 of the 240 patients (9%) were over the age of 65. In general, dose selection for an elderly patient should be made with caution, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: In controlled, clinical trials with CLOBEX® (clobetasol propionate) Spray, 0.05%, the most common adverse reaction was burning at the site of application [40% of subjects treated with CLOBEX® (clobetasol propionate) Spray, 0.05% and 47% of subjects treated with Spray Vehicle]. Other commonly reported adverse reactions for CLOBEX® (clobetasol propionate) Spray, 0.05% and Spray Vehicle, respectively, are noted in Table 2.

Table 2 – Commonly Occurring Adverse Events

Adverse Reaction	Clobetasol Propionate 0.05% Spray (N=120)	Vehicle Spray (N=120)
System Organ Class		
General disorders and administration site conditions	50 (42%)	56 (47%)
Application site atrophy	0 (0%)	1 (1%)
Application site burning	48 (40%)	56 (47%)
Application site dryness	2 (2%)	0 (0%)
Application site irritation	1 (1%)	0 (0%)
Application site pain	1 (1%)	2 (2%)
Application site pigmentation changes	1 (1%)	0 (0%)
Application site pruritus	4 (3%)	3 (3%)
Infections and infestations	17 (14%)	12 (10%)
Influenza	0 (0%)	2 (2%)
Nasopharyngitis	6 (5%)	3 (3%)
Pharyngitis streptococcal	1 (1%)	0 (0%)
Upper respiratory tract infection	10 (8%)	2 (2%)

Skin and subcutaneous tissue disorders	4 (3%)	2 (2%)
Eczema asteatotic	2 (2%)	0 (0%)

Other adverse events occurred at rates less than 1.0%. Most local adverse events were rated as mild to moderate and they are not affected by age, race or gender. The following additional local adverse reactions have been reported with topical corticosteroids. They may occur more frequently with the use of occlusive dressings and higher potency corticosteroids, including clobetasol propionate. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae and miliaria.

Systemic absorption of topical corticosteroids has produced hypothalamic-pituitary-adrenal (HPA) axis suppression manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

OVERDOSAGE: Topically applied CLOBEX® (clobetasol propionate) Spray, 0.05% can be absorbed in sufficient amount to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION: CLOBEX® (clobetasol propionate) Spray, 0.05% should be sprayed directly onto the affected skin areas twice daily and rubbed in gently and completely (see INDICATIONS AND USAGE.).

CLOBEX® (clobetasol propionate) Spray, 0.05% contains a super-high potent topical corticosteroid; therefore treatment should be limited to 4 weeks. Treatment beyond 2 weeks should be limited to localized lesions of moderate to severe plaque psoriasis that have not sufficiently improved after the initial 2 weeks of treatment with CLOBEX® (clobetasol propionate) Spray, 0.05%.

The total dosage should not exceed 50 g (59 mL or 2 fluid ounces) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Use in pediatric patients younger than 18 years is not recommended because of the potential for HPA axis suppression (see PRECAUTIONS: Pediatric Use).

Unless directed by physician, CLOBEX® (clobetasol propionate) Spray, 0.05% should not be used with occlusive dressings.

HOW SUPPLIED: CLOBEX® (clobetasol propionate) Spray, 0.05% is supplied in 2-oz white HDPE bottle with white polypropylene cap and white LDPE liner.

Store under controlled room temperature conditions of 20°C – 25°C (68°F- 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F). Do not freeze, refrigerate or store above 30° C. Spray is flammable; keep away from heat or flame.

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