HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use hydrocortisone butyrate cream, 0.1% (lipophilic) safely and effectively. See full prescribing information for hydrocortisone butyrate cream, 0.1% (lipophilic).

HYDROCORTISONE BUTYRATE Cream, 0.1% (Lipophilic)
For topical use only
Initial U.S. Approval: 1982

INDICATIONS AND USAGE
Hydrocortisone butyrate cream, 0.1% (lipophilic) is a topical corticosteroid indicated for:
1. Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults. (1.1)
2. The treatment of mild to moderate atopic dermatitis in patients 3 months to 18 years of age. (1.2)

DOSE AND ADMINISTRATION
• Hydrocortisone butyrate cream, 0.1% (lipophilic) is not for oral, ophthalmic, or intravaginal use. (2)
• Apply a thin film to the affected skin areas two or three times daily for corticosteroid-responsive dermatoses in adults. (2)
• Apply a thin film to the affected skin areas two times daily for atopic dermatitis in patients 3 months of age and older. (2)
• Apply a thin film to the affected skin areas three times daily for corticosteroid-responsive dermatoses in children. (2)
• Discontinue hydrocortisone butyrate cream, 0.1% (lipophilic) when control is achieved. (2)
• Reassess diagnosis if no improvement is seen within 2 weeks. 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 and local adverse events. Safety and efficacy of hydrocortisone butyrate cream, 0.1% (lipophilic) has not been established beyond weeks 4. (4)

ADVERSE REACTIONS
• HPA axis suppression: (6.1)
• Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if hydrocortisone butyrate cream is applied to large surface areas or used under occlusion. If HPA axis suppression is noted, reduce the application frequency, discontinue use, or switch to a lower potency corticosteroid. (5.1, 8.4)
• Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. (5.1, 8.4)
• Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body-mass ratios. (5.1, 8.4)
• Infinitive appropriate therapy if concomitant skin infections develop. (5.2)
• Discontinue use if irritation develops. (5.3)

ADVERSE REACTIONS
The most common adverse reactions (≥1%) are HPA axis suppression and application site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Glenmark Pharmaceuticals Inc., USA at 1 (888) 721-7115 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
Based on animal data, may cause fetal harm. (8.1)

See 17 FOR PATIENT COUNSELING INFORMATION.

Revised: 09/2014

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Corticosteroid-Responsive Dermatoses in Adults
2.2 Atopic Dermatitis in Patients From 3 Month to 18 Years
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypothalamic-Pharyngeal-Adrenal (HPA) Axis Suppression
5.2 Concomitant Skin Infections
5.3 Skin Irritation
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience: Adults
6.2 Clinical Trials Experience: Pediatrics
6.3 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Nursing Mothers
8.3 Pediatric Use
8.4 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility
14 CLINICAL STUDIES
14.2 Pediatric Atopic Dermatitis
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

5.3 Skin Irritation
Hydrocortisone butyrate may cause local skin adverse reactions [see Adverse Reactions (6)]. If irritation develops, hydrocortisone butyrate should be discontinued and appropriate therapy instituted. Alcoholic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noticing a clinical exacerbation. Such an observation should be corroborated with appropriate patch testing.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
• HPA axis suppression: (6.1)
• Concomitant skin infections (see Warnings and Precautions (5.2))
• Skin irritation (see Warnings and Precautions (5.3))

6.1 Clinical Trials Experience: Adults
The following additional local adverse reactions have been reported infrequently with topical corticosteroids but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, drying, miliaria, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, irritant and inductive.

6.2 Clinical Trials Experience: Pediatrics
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. The safety data derived from hydrocortisone butyrate clinical trials reflect exposure to hydrocortisone butyrate twice daily for up to four weeks in separate clinical trials involving pediatric subjects 3 months to 18 years of age with mild to moderate atopic dermatitis.

Adverse reactions shown in the tables below include those for which there is some basis to believe there is a causal relationship to hydrocortisone butyrate.

Table 1. Frequency of adverse reactions in pediatric subjects with mild to moderate atopic dermatitis

<table>
<thead>
<tr>
<th>Hydrocortisone butyrate (N=37)</th>
<th>Vehicle (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site reactions, including application site folliculitis, lichen, dermatitis, or erythema</td>
<td>1.5%</td>
</tr>
<tr>
<td>Acne</td>
<td>0.8%</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

6.3 Postmarketing Experience
The following adverse reactions have been identified during post approval use of hydrocortisone butyrate. 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.

SKIN Erythema, rash and application site irritation.

7 DRUG INTERACTIONS
There are no known drug interactions with hydrocortisone butyrate.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Hydrocortisone butyrate should not be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Corticosteroids have been shown to be teratogenic in laboratory animals when administered to rats and rabbits at pharmacologically effective doses. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Note: The animal models of human carcinogenesis have not been shown to be predictive of potential carcinogenic risk to humans. Long-term studies in animals are conducted over a period of 2 years in rats and many months in mice.

8.2 Lactation

Hydrocortisone butyrate is not excreted in human milk, and breast-feeding should not be recommended unless the potential benefit to the infant justifies the potential risk to the mother.

8.3 Children

No reliable data are available regarding the use of topical corticosteroids in children. The use of corticosteroids in the management of atopic dermatitis of infancy, which affects predominantly infants and young children, has been well documented. The safety and efficacy of hydrocortisone in children have not been established. Therefore, it is recommended that children not be treated with corticosteroids for longer than necessary.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below 3 months of age have not been established.

Because hydrocortisone is used primarily on the skin to treat inflammatory and pruritic conditions, systemic absorption is unlikely, with the possible exception of newborns and infants. Systemic absorption is not a safety concern in children. The safety and efficacy of hydrocortisone in children have not been established. Therefore, it is recommended that children under 3 months not be treated with corticosteroids for longer than necessary.

8.5 Geriatric Use

Clinical studies of hydrocortisone butyrate did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Hydrocortisone butyrate cream, 0.1% (ophthalmic) contains hydrocortisone butyrate USP, a non-fluorinated hydrocortisone ester [Phage 4-ene-3-one 3,2-dione, 11, 21-dihydroxy-17- (11-oxobutyloxy) C30H36O6] for topical dermatologic use.

Chemically, hydrocortisone butyrate USP is C29H31O6. It has the following structural formula.

11.1.1...

Hydrocortisone butyrate USP is a white to practically white powder with a molecular weight of 432.56. It is practically insoluble in water, slightly soluble in ether, soluble in methanol, in alcohol, and in acetone, and freely soluble in chloroform.

Each gram of hydrocortisone butyrate USP, 0.1% (ophthalmic) contains 1 mg hydrocortisone butyrate USP, equal in base to containing of cetomethanol, alurial 1/60 (glycerol/stearate and PE 100 steareate), mineral oil, white petroleum, sulfuric monostearate, arachidonic acid, sodium citrate, hydrophilic, propylene, benzyl alcohol and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Topical corticosteroids share anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical corticosteroids is unclear. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potential 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.

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 can be absorbed through normal intact skin. Inflammation and/or other disease processes in the skin, occlusive dressings, or widespread application may increase percutaneous absorption and increase the risk of HPA Axon suppression.

The vasoconstrictor assay showed that hydrocortisone butyrate cream, 0.1% (ophthalmic) had a more pronounced skin blanching effect than hydrocortisone butyrate cream, 0.1%, suggesting greater percutaneous absorption from the former.

These absorbed through the skin, topical corticosteroids are handled through pharmaceutics pathways similar to systemically administered corticosteroids.

Corticosteroids are bound to plasma proteins in varying degrees.

Some of the topical corticosteroids and their metabolites are also excreted into the bile.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies were conducted to determine the photocarcinogenic or dermal carcinogenic potential of hydrocortisone butyrate.

Hydrocortisone butyrate revealed no evidence of mutagenicity or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames test and L5178Y TK+/mouse lymphoma assay) and one in vivo mutagenicity test (Salmonella typhimurium assay).

No evidence of impairment of fertility or effect on mating performance was observed in a fertility and general reproductive performance study conducted in male and female rats at subcutaneous doses up to 1 mg/kg/day (0.7X MHD) and 0.1 mg/kg/day (0.07X MHD) on gestation days 2–18. Fertility was unaffected at any of the dose levels (0.1 X – 13X MHD).

14 CLINICAL STUDIES

14.2 Pediatric Atopic Dermatitis

In a multicenter, randomized, vehicle-controlled trial of 264 pediatric subjects 3 to 18 years of age with mild to moderate atopic dermatitis, hydrocortisone butyrate or vehicle was applied twice daily for 4 weeks. Treatment success was assessed at day 29 (after 28 days of treatment) and was defined as the proportion of patients who achieved both “clear” or “almost clear” and at least a two grade improvement from baseline on a 5-point Physician’s Global Assessment (PGA) scale. Study results are shown in Table 2.

Table 2: Efficacy Results at Day 29 in Pediatric Subjects

<table>
<thead>
<tr>
<th>Hydrocortisone butyrate</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=131)</td>
<td>(n=130)</td>
</tr>
<tr>
<td>Number (%) successes</td>
<td>82 (62%)</td>
</tr>
<tr>
<td>15 g NDC 68458-464-15</td>
<td>45 g NDC 68458-464-47</td>
</tr>
<tr>
<td>Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]</td>
<td>Protect from freezing. Keep out of the reach of children.</td>
</tr>
</tbody>
</table>

17 PATIENT COUNSELING INFORMATION

Patients using hydrocortisone butyrate should receive the following information and instructions:

• Discontinue hydrocortisone butyrate when control is achieved.
• Apply a thin film to the affected skin areas two or three times daily for corticosteroid-responsive dermatitis in adults.
• Assess your physician to determine if treatment is needed beyond 2 weeks.
• Apply a thin film to the affected skin areas two days daily for atopic dermatitis in patients 3 months of age and older. Safety of hydrocortisone butyrate in pediatric patients has not been established beyond 4 weeks of use.
• Rub in gently.
• Avoid contact with the eyes.
• Do not bandage, otherwise, cover, or wrap the affected skin area so as to be completely until desired by your physician.
• Do not use corticosteroid cream in the diaper area, as diapers or plastic pants may constitute occlusive dressings.
• Do not use any corticosteroids in the diaper area, on the umbilicus, or groin areas unless directed by your physician.
• If irritation or improvement is seen within 2 weeks, contact your physician.
• Do not use other corticosteroid-containing products while using hydrocortisone butyrate without first consulting your physician.

Manufactured by:

Gleneagles Pharmaceuticals Ltd. 
Village Khairapana, Barad Nangal Road 
District: Solan, Himachal Pradesh — 173205, India

Manufactured for:

Gleneagles Pharmaceuticals Inc., USA
Mahwah, NJ 07430

Questions? 1-888-271-7155

www.gleneaglespharma.com

September 2014