# DUOBRII- halobetasol propionate and tazarotene lotion
**Bausch Health US, LLC**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use DUOBRII safely and effectively. See full prescribing information for DUOBRII.**

**DUOBRII® (halobetasol propionate and tazarotene) lotion, for topical use**
**Initial U.S. Approval: 2019**

**INDICATIONS AND USAGE**

DUOBRII Lotion is a combination of halobetasol propionate and tazarotene indicated for the topical treatment of plaque psoriasis in adults. (1)

**DOSAGE AND ADMINISTRATION**

- Apply a thin layer of DUOBRII Lotion to the affected areas once daily. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

**DOSAGE FORMS AND STRENGTHS**

Lotion, 0.01%/0.045% (3)
Each gram of DUOBRII Lotion contains 0.1 mg (0.01%) halobetasol propionate and 0.45 mg (0.045%) tazarotene. (3)

**CONTRAINDICATIONS**

DUOBRII Lotion is contraindicated in pregnancy (4.1, 8.1)

**WARNINGS AND PRECAUTIONS**

- *Embryofetal risk*: DUOBRII Lotion contains tazarotene, which is a teratogenic substance. In females of reproductive potential, obtain a negative pregnancy test within 2 weeks prior to initiating treatment and advise patients to use an effective method of contraception during treatment. (5.1)
- Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency during or after treatment. (5.2)
- Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. (5.2)
- Systemic absorption may require evaluation for HPA axis suppression. (5.2)
- Use of potent corticosteroids on large areas, for prolonged durations, under occlusive dressings, or on an altered skin barrier may increase systemic exposure. (5.2)
- *Local Adverse Reactions*: Local adverse reactions may include atrophy, striae, telangiectasias, and folliculitis. If these effects occur, discontinue at least until the integrity of the skin has been restored. DUOBRII Lotion should not be used on eczematous skin, as it may cause severe irritation. (5.3)
- *Photosensitivity and Risk for Sunburn*: Avoid exposure to sunlight, sunlamps, and weather extremes. DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers. (5.4)
- *Ophthalmic Adverse Reactions*: Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist (5.5).

**ADVERSE REACTIONS**

- The most common adverse reactions are contact dermatitis (7%), application site pain (3%), folliculitis (2%), skin atrophy (2%), and excoriation (2%). (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**
**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 1/2020**

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## FULL PRESCRIBING INFORMATION: CONTENTS*

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

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

DUOBRII® (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% is indicated for the topical treatment of plaque psoriasis in adults.

### 2 DOSAGE AND ADMINISTRATION

Apply a thin layer of DUOBRII Lotion once daily to cover only affected areas and rub in gently. If a bath or shower is taken prior to application, the skin should be dry before applying the lotion.

The total dosage should not exceed approximately 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis *[see Warnings and Precautions (5.2)]*. Do not use with occlusive dressings unless directed by a physician. Discontinue treatment when control is achieved. Avoid application of DUOBRII Lotion on the face, groin, or in the axillae.

DUOBRII Lotion is not for oral, ophthalmic, or intravaginal use.

## 3 DOSAGE FORMS AND STRENGTHS

Lotion, 0.01%/0.045%

Each gram of DUOBRII Lotion contains 0.1 mg (0.01%) halobetasol propionate and 0.45 mg (0.045%) tazarotene in a white to off-white lotion.

## 4 CONTRAINDICATIONS

### 4.1 Pregnancy

DUOBRII Lotion is contraindicated in pregnancy [*see Warnings and Precautions* (5.1), *Use in Specific Populations* (8.1, 8.3)].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Embryofetal Risk

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Tazarotene is teratogenic, and it is not known what level of exposure is required for teratogenicity in humans *[see Contraindications (4), Clinical Pharmacology (12.3)]*. Tazarotene elicits teratogenic and developmental effects associated with retinoids after topical or systemic administration in rats and rabbits *[see Use in Specific Populations (8.1)]*.

Advise pregnant females of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to DUOBRII Lotion therapy. Initiate DUOBRII Lotion therapy during a menstrual period. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion therapy *[see Use in Specific Populations (8.1 and 8.3)]*.

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

DUOBRII Lotion contains halobetasol propionate, a corticosteroid, and has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment of the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with DUOBRII Lotion was evaluated in a study of 20 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area. The subjects were treated once daily for 8 weeks and assessed for HPA axis suppression at Weeks 4 and 8. HPA axis suppression occurred in 3 out of 20 (15%) subjects at Week 4 and none (0%) of these 20 subjects had HPA axis suppression at Week 8 *[see Clinical Pharmacology (12.2)]*.

Because of the potential for systemic absorption, use of topical corticosteroids, including DUOBRII Lotion, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug or reduce the frequency of application. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation

of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to topical corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids because of their larger surface-to-body-mass ratio *[see Use in Specific Populations (8.4)]*.

### 5.3 Local Adverse Reactions

Local adverse reactions may include atrophy, striae, telangiectasias, folliculitis and contact dermatitis. Some local adverse reactions may be irreversible. If these adverse reactions occur, discontinue the medication at least until the integrity of the skin is restored; do not resume treatment if allergic contact dermatitis is identified.

Avoid use of DUOBRII Lotion on eczematous skin, as it may cause severe irritation.

### 5.4 Photosensitivity and Risk for Sunburn

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of DUOBRII Lotion. Patients must be instructed to use sunscreens and protective clothing when using DUOBRII Lotion. Patients with sunburn should be advised not to use DUOBRII Lotion until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using DUOBRII Lotion.

DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

### 5.5 Ophthalmic Adverse Reactions

Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported postmarketing with the use of topical corticosteroid products. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

### 5.6 Concomitant Skin Infections

Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of DUOBRII Lotion until the infection has been adequately treated.

## 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.

In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 410 adults with plaque psoriasis were treated with DUOBRII Lotion or vehicle lotion and had post-baseline safety data. Subjects applied DUOBRII Lotion or vehicle lotion once daily for up to 8 weeks. Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with DUOBRII Lotion and more frequently than in vehicle-treated subjects.

**Table 1: Adverse Reactions Occurring in ≥1% of the Subjects Treated with DUOBRII Lotion**

**through Week 8**

| Adverse Reaction | DUOBRII Lotion (N=270) | Vehicle Lotion (N=140) |
|---|---|---|
| Contact Dermatitis | 20 (7%) | 0 |
| Application Site Pain | 7 (3%) | 1 (1%) |
| Folliculitis | 5 (2%) | 0 |
| Skin Atrophy | 5 (2%) | 0 |
| Excoriation | 5 (2%) | 0 |
| Rash | 4 (1%) | 0 |
| Skin Abrasion | 3 (1%) | 0 |
| Skin Exfoliation | 2 (1%) | 0 |

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Risk Summary*

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Safety in pregnant females has not been established. The potential risk to the fetus outweighs the potential benefit to the mother from DUOBRII Lotion during pregnancy; therefore, DUOBRII Lotion should be discontinued as soon as pregnancy is recognized *[see Contraindications (4), Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

Observational studies suggest an increased risk of low birthweight in infants with the maternal use of potent or very potent topical corticosteroids (*see Data*).

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose 11 times the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 116 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 9 and 228 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 9 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during the period of organogenesis to pregnant rats and rabbits *(see Data)*. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of DUOBRII Lotion.

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

*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*

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (11 times the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation (0.5%, 0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (116 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 9 and 228 times, respectively, the MRHD (based on AUC comparisons).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (16 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at that dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to 5 times the MRHD (based on AUC comparison).

**8.2 Lactation**

*Risk Summary*

There are no data on the presence of tazarotene, halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with DUOBRII Lotion.

After single topical doses of a $^{14}$C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk.

It is not known whether topical administration of 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 DUOBRII Lotion and any potential adverse effects on the breastfed child from DUOBRII Lotion.

*Clinical Considerations*

Advise breastfeeding women not to apply DUOBRII Lotion directly to the nipple and areola to avoid direct infant exposure.

### 8.3 Females and Males of Reproductive Potential

*Pregnancy Testing*

DUOBRII Lotion is contraindicated in women who are pregnant. Females of reproductive potential should be warned of the potential risk and use adequate birth control measures during treatment with DUOBRII Lotion. The possibility that a female of reproductive potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy should be obtained within 2 weeks prior to DUOBRII Lotion therapy, which should begin during menstruation.

*Contraception*

Based on animal studies, DUOBRII Lotion may cause fetal harm when administered to a pregnant female *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion.

### 8.4 Pediatric Use

Safety and effectiveness of DUOBRII Lotion in pediatric patients under the age of 18 years have not been evaluated.

Because of higher skin-surface-area-to-body-mass ratios, 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 adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children *[see Warnings and Precautions (5.2)]*.

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 an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema *[see Warnings and Precautions (5.2)]*.

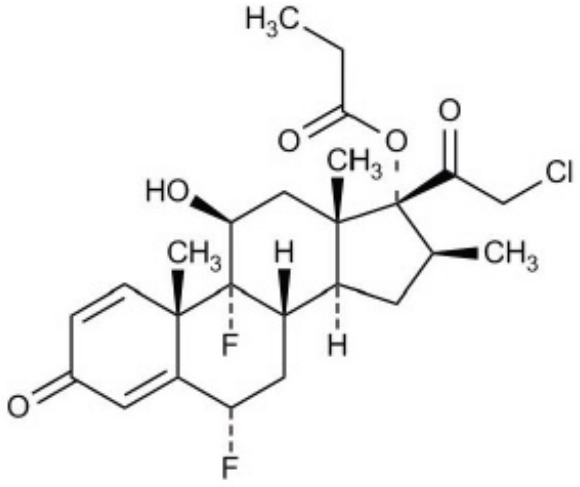
### 8.5 Geriatric Use

Of the 270 subjects exposed to DUOBRII Lotion in clinical trials, 39 subjects were 65 years or older. Clinical trials of DUOBRII Lotion did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

## 11 DESCRIPTION

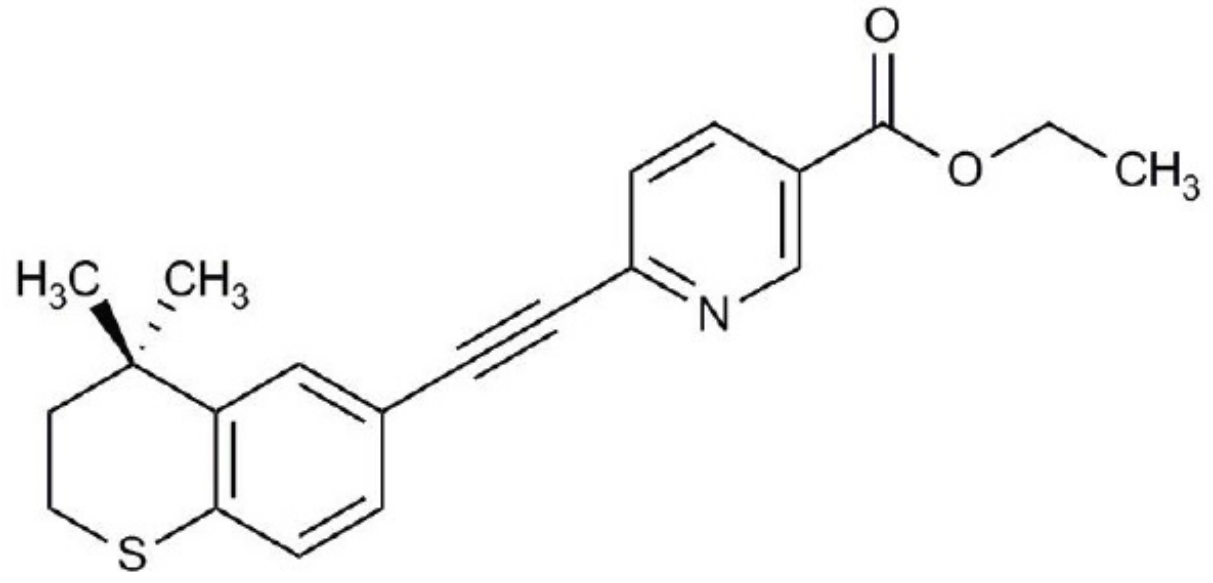
DUOBRII Lotion is a combination product with halobetasol propionate and tazarotene as the active ingredients in a white to off-white lotion formulation intended for topical use.

Halobetasol propionate is a synthetic corticosteroid. The chemical name for halobetasol propionate is [(6S,9R,16S,17R)-17-(2-chloroacetyl)-6,9-difluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] propanoate. The structural formula for halobetasol propionate is represented below:



Molecular Formula: $C_{25}H_{31}ClF_2O_5$ Molecular Weight: 484.96

Tazarotene is a member of the acetylenic class of retinoids. The chemical name for tazarotene is 6-[(3,4-Dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl]-3-pyridinecarboxylic acid ethyl ester. The structural formula for tazarotene is represented below:



Molecular Formula: $C_{21}H_{21}NO_2S$ Molecular Weight: 351.46

Each gram of DUOBRII Lotion contains 0.1 mg (0.01%) halobetasol propionate and 0.45 mg (0.045%)

tazarotene in a white to off-white lotion base consisting of carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%.

## 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 in plaque psoriasis is unknown.

Tazarotene is a retinoid prodrug which is converted to its active form, tazarotenic acid, the carboxylic acid of tazarotene, by deesterification. Tazarotenic acid binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings for the treatment of plaque psoriasis is unknown.

### 12.2 Pharmacodynamics

A vasoconstrictor assay in healthy subjects with DUOBRII Lotion indicated that it is in the high to super-high range of potency as compared to other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression was evaluated in a study in adult subjects with moderate to severe plaque psoriasis. A median dose of 8.2 grams DUOBRII Lotion was applied once daily for 8 weeks and 20 subjects were assessed for HPA axis suppression at Weeks 4 and 8. HPA axis suppression was observed in 3 out of 20 (15%) subjects at Week 4. None of the 20 (0%) subjects had HPA axis suppression at Week 8. In this study, the criteria for HPA axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation with cosyntropin (adrenocorticotropic hormone). *[See Warnings and Precautions (5.2).]*

The pharmacodynamics of tazarotene is unknown.

### 12.3 Pharmacokinetics

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid.

Systemic exposure following topical application of DUOBRII Lotion was evaluated in the same study that evaluated the HPA axis suppression. It was an open-label, randomized, pharmacokinetics (PK) study conducted in subjects aged 18 years and older with moderate to severe plaque psoriasis affecting at least 20% body surface area. The PK of halobetasol propionate, tazarotene, and tazarotenic acid was evaluated in 22 subjects following application of DUOBRII Lotion to the affected area once daily for 28 days. Systemic concentrations of halobetasol propionate (lower limit of quantification (LLOQ) = 50 pg/mL) and tazarotene (LLOQ = 5 pg/mL) on Day 28 were quantifiable in 13 and 18 out of a total number of 22 subjects, respectively. Tazarotenic acid (LLOQ = 5 pg/mL) was quantifiable in all subjects. Systemic exposure of the three moieties was at or near steady state by Day 28. The mean (standard deviation) of PK parameters on Day 28 is shown in Table 2.

**Table 2:PK Parameters of Halobetasol Propionate, Tazarotene, and Tazarotenic Acid Following Once Daily Administration of DUOBRII Lotion for 28 Days in Subjects with Moderate to Severe Plaque Psoriasis**

| | | Mean (Standard Deviation) (N=22) | | |
|---|---|---|---|---|
| | **PK Parameters** | **Halobetasol Propionate** | **Tazarotene** | **Tazarotenic Acid** |
| | $C_{ss}$ (pg/mL) | 101.9 (135.4) | 24.6 (27.3) | 523.4 (523.3) |

| | | | | |
|---|---|---|---|---|
| **Day 28** | $C_{max}$ (pg/mL) | 101.9 (135.4) | 24.6 (27.3) | 323.4 (323.3) |
| | $AUC_{0-24}$ (pg*hr/mL) | 1300 (1959) | 273 (403) | 9954 (10091) |

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 1.4 times the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposures at the highest dose was 35 times the MRHD (based on AUC comparison).

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day, approximately 0.53 times the MRHD based on BSA comparisons, indicated no impairment of fertility or general reproductive performance.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was 5 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene, which produced a systemic exposure 17 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose, which produced a systemic exposure 30 times the MRHD (based on AUC comparison).

## 14 CLINICAL STUDIES

The safety and efficacy of once daily use of DUOBRII Lotion for the treatment of moderate to severe plaque psoriasis were assessed in two prospective, multicenter, randomized, double-blind clinical trials (Trial 1 [NCT02462070] and Trial 2 [NCT02462122]). These trials were conducted in 418 subjects 18 years of age and older with moderate to severe plaque psoriasis that covered a body surface area (BSA) between 3% and 12% excluding the face, scalp, palms, soles, axillae, and intertriginous areas. Disease severity was determined by a 5-grade Investigator’s Global Assessment (IGA). Subjects

applied DUOBRII Lotion or vehicle to all affected areas once daily for up to 8 weeks. All subjects returned for a 4-week follow-up visit (Week 12 visit) where safety and efficacy were evaluated.

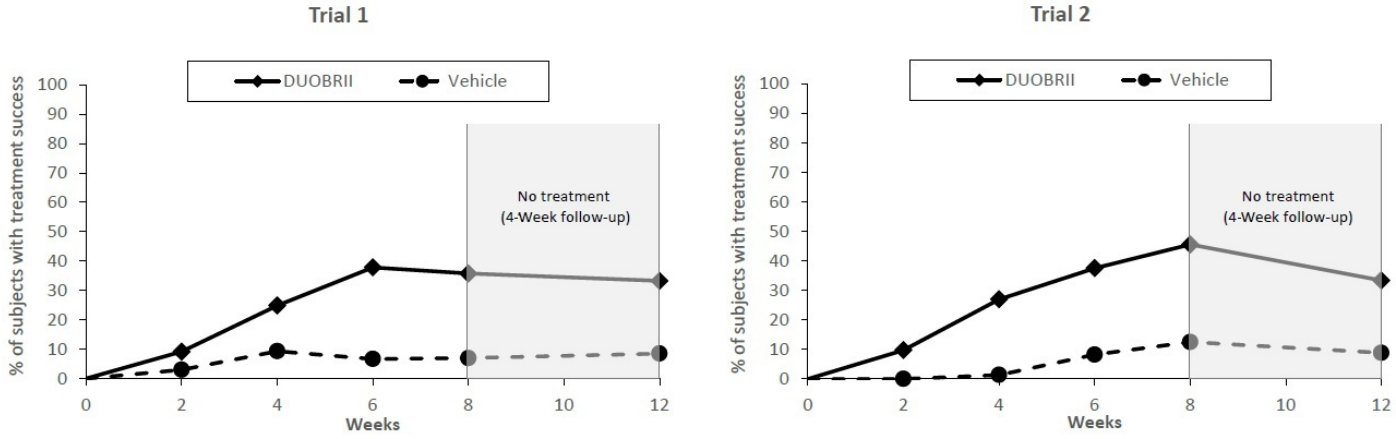
The primary efficacy endpoint was the proportion of subjects with "treatment success" at Week 8. Treatment success was defined as at least a 2-grade improvement from baseline in the IGA score and an IGA score equating to "clear" or "almost clear". Table 3 lists the primary efficacy results for Trials 1 and 2. The secondary efficacy endpoints evaluated treatment success sequentially at Weeks 12, 6, 4, and 2. Figure 1 shows the primary and secondary efficacy results over time.

**Table 3: Primary Efficacy Outcomes in Subjects with Moderate to Severe Plaque Psoriasis at Week 8**

| | Trial 1 | | Trial 2 | |
|---|---|---|---|---|
| | DUOBRII | Vehicle | DUOBRII | Vehicle |
| | N=135 | N=68 | N=141 | N=74 |
| IGA Treatment Success at Week 8* | 36% | 7% | 45% | 13% |

* Treatment success was defined as at least a 2-grade improvement from baseline in IGA score and an IGA score equating to "clear" or "almost clear". Clear = no evidence of scaling, no evidence of erythema, no evidence of plaque elevation above normal skin level. Almost clear = some plaques with fine scales, faint pink/light red erythema on most plaques, slight or barely perceptible elevation of plaques above normal skin level.

Figure 1: Efficacy Results* over Time




*The treatment difference at Week 2 in Trial 1 was not statistically significant.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

DUOBRII (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% is a white to off-white lotion supplied in a white aluminum tube as follows:

- 100 g (NDC 0187-0653-01)

### Storage and Handling Conditions

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.

## 17 PATIENT COUNSELING INFORMATION

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

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all administration instructions or all possible adverse or unintended effects.

Advise patients using DUOBRII Lotion of the following information and instructions:

**Important Administration Instructions**

If undue irritation (redness, peeling, or discomfort) occurs, reduce frequency of application or temporarily interrupt treatment. Treatment may be resumed once irritation subsides [*see Dosage and Administration (2) and Warnings and Precautions (5.2)*].

Inform patients that total dosage should not exceed 50 grams per week *[see Dosage and Administration (2)]*.

Instruct patients to avoid bandaging, wrapping or otherwise occluding the treatment area(s), unless directed by physician. Advise patients to avoid use on the face, groin, or axillae *[see Dosage and Administration (2)]*.

Inform patients that DUOBRII Lotion is for external use only. Advise patients that DUOBRII Lotion is not for oral, ophthalmic, or intravaginal use *[see Dosage and Administration (2)]*.

Fetal risk is associated with DUOBRII Lotion for females of reproductive potential. Advise patients to use an effective method of contraception during treatment to avoid pregnancy. Advise the patient to stop medication if she becomes pregnant and call her doctor [*see Contraindications (4.1), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

Breastfeeding women should not apply DUOBRII Lotion directly to the nipple and areola to avoid directly exposing the infant *[see Use in Specific Populations (8.2)]*.

Avoid exposure of the treated areas to either natural or artificial sunlight, including tanning beds and sunlamps. Use sunscreen and protective clothing if exposure to sunlight is unavoidable when using DUOBRII Lotion *[see Warnings and Precautions (5.4)]*.

**HPA Axis Suppression and Other Unwanted Systemic Glucocorticoid Effects**

DUOBRII Lotion may cause HPA axis suppression. Advise patients that use of topical corticosteroids, including DUOBRII Lotion, may require periodic evaluation for HPA axis suppression. Topical corticosteroids may have other endocrine effects. Concomitant use of multiple corticosteroid-containing products may increase the total systemic exposure to topical corticosteroids *[see Warnings and Precautions (5.2)]*.

**Local Adverse Reactions**

Inform patients that DUOBRII Lotion may cause local adverse reactions. These reactions may be more likely to occur with occlusive use or use of DUOBRII Lotion. If undue irritation (redness, peeling, or discomfort) occurs, reduce frequency of application or temporarily interrupt treatment. Treatment may be resumed once irritation subsides, unless allergic contact dermatitis is identified *[see Warnings and Precautions (5.3)]*.

**Ophthalmic Adverse Reactions**

Advise patients to report any visual symptoms to their healthcare providers.

**Distributed by:**
Bausch Health US, LLC
Bridgewater, NJ 08807 USA

**Manufactured by:**
Bausch Health Companies Inc.

Laval, Quebec H7L 4A8, Canada

U.S. Patent Numbers: 6,517,847; 8,809,307; 10,251,895 and 10,478,502

DUOBRII is a trademark of Bausch Health Companies Inc. or its affiliates.



9645602

**Patient Package Insert**

TEAR HERE (Patient Inforamtion)

**PATIENT INFORMATION**
**DUOBRII® (DEW-oh-bree)**
**(halobetasol propionate and tazarotene) lotion, for topical use**

**Important information: DUOBRII is for use on skin only.** Do not apply DUOBRII in your mouth, eyes, or vagina.

**What is the most important information I should know about DUOBRII?**

**DUOBRII may cause birth defects if used during pregnancy.**
**Females must not be pregnant when they start using DUOBRII or become pregnant during treatment with DUOBRII.**

- For females who are able to get pregnant:
    - Your healthcare provider will order a pregnancy test for you within 2 weeks before you begin treatment with DUOBRII to be sure that you are not pregnant. Your healthcare provider will decide when to do the test.
    - Begin treatment with DUOBRII during a normal menstrual period.
    - Use an effective form of birth control during treatment with DUOBRII. Talk with your healthcare provider about birth control options that may be used to prevent pregnancy during treatment with DUOBRII.
    - **Stop using DUOBRII and tell your healthcare provider right away if you become pregnant during treatment with DUOBRII.**

**What is DUOBRII?**

DUOBRII is a prescription medicine used on the skin (topical) to treat adults with plaque psoriasis.
It is not known if DUOBRII is safe and effective in children under 18 years of age.

**Do not use DUOBRII if you:**

- are pregnant. See **“What is the most important information I should know about DUOBRII?”**

**Before using DUOBRII, tell your healthcare provider about all of your medical conditions, including if you:**

- have eczema or any other skin problems.
- have a skin infection. You may need medicine to treat the skin infection before using DUOBRII.
- have diabetes.
- have adrenal gland problems.
- have liver problems.

- are breastfeeding or plan to breastfeed. It is not known if DUOBRII passes into your breast milk. If you use DUOBRII and breastfeed, do not apply DUOBRII to your nipple or areola to avoid getting DUOBRII into your baby's mouth.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements.

**Especially tell your healthcare provider if you take** corticosteroids by mouth, or injection, or use other products on your skin that contain corticosteroids.

**Certain medicines may make your skin more sensitive to sunlight.** Ask your healthcare provider for a list of these medicines if you are not sure.

**How should I use DUOBRII?**

- Use DUOBRII exactly as your healthcare provider tells you to use it.
- If you shower or bathe before applying DUOBRII, your skin should be dry before applying the lotion.
- Apply a thin layer of DUOBRII to the affected areas 1 time each day and rub in gently.
- You should not use more than 50 grams of DUOBRII in 1 week.
- Avoid using DUOBRII on your face, groin, or underarms (armpits).
- Do not bandage, wrap, or cover the treated skin area(s) unless your healthcare provider tells you to.

**What should I avoid during treatment with DUOBRII?**

- Avoid sunlight, including sunlamps and tanning beds during your treatment with DUOBRII. DUOBRII can make your skin more sensitive to the sun and the light from sunlamps and tanning beds. You could get severe sunburn. Use sunscreen, and wear a hat and clothes that cover your skin if you have to be in sunlight.
- Talk to your healthcare provider if you get sunburn during treatment with DUOBRII. If you do get sunburn, do not use DUOBRII until your sunburn is healed.
- Avoid using DUOBRII on skin with eczema because it may cause severe irritation.

**What are the possible side effects of DUOBRII?**

**DUOBRII may cause side effects, including:**

- See **"What is the most important information I should know about DUOBRII?"**
- **DUOBRII can pass through your skin.** Too much DUOBRII passing through your skin can cause adrenal glands to stop working.
- **Cushing's syndrome**, a condition that happens when your body is exposed to too much of the hormone cortisol.
- **High blood sugar** (hyperglycemia).
- **Effects of growth and weight in children.**
- **Skin irritation**. DUOBRII may cause increased skin irritation. Tell your healthcare provider if you develop any skin irritation during your treatment with DUOBRII. If you develop skin irritation, your healthcare provider may tell you to interrupt or stop using DUOBRII, or tell you to use DUOBRII less often.
- **Sensitivity to light and risk of sunburn.** See **"What should I avoid during treatment with DUOBRII?"**
- **Vision problems.** DUOBRII may increase your chance of developing cataract(s) and glaucoma. Tell your healthcare provider if you have blurred vision or other vision problems during your

treatment with DUOBRII.

**The most common side effects of DUOBRII include:** redness, itching, swelling, burning, stinging, application site pain, inflamed hair follicles (folliculitis), thinning of the skin (atrophy), peeling and rash.

These are not all of the possible side effects of DUOBRII.

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 DUOBRII?**

- Store DUOBRII at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect from freezing.

**Keep DUOBRII and all medicines out of the reach of children.**

**General information about the safe and effective use of DUOBRII**

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

**What are the ingredients in DUOBRII?**

**Active ingredients:** halobetasol propionate and tazarotene

**Inactive ingredients:** carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%.

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U.S. Patent Numbers: 6,517,847; 8,809,307; 10,251,895 and 10,478,502

DUOBRII is a trademark of Bausch Health Companies Inc. or its affiliates.



For more information call 1-800-321-4576

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

Revised: 01/2020

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**Package/Label Display Panel**

**NDC** 0187-0653-01

**Duobrii®**
**(halobetasol propionate**
**and tazarotene) Lotion**
**0.01%/0.045%**

**Rx only**
**Net Wt. 100g**

**For Topical Use Only**

**Not for Eye Use**

**Ortho** Dermatologics


# DUOBRII

halobetasol propionate and tazarotene lotion

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:0187-0653 |
| **Route of Administration** | TOPICAL | | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **HALOBETASOL PROPIONATE** (UNII: 91A0K1TY3Z) (HALOBETASOL - UNII:9P6159HM7T) | HALOBETASOL PROPIONATE | 0.1 mg in 1 g |
| **TAZAROTENE** (UNII: 81BDR9Y8PS) (TAZAROTENE - UNII:81BDR9Y8PS) | TAZAROTENE | 0.45 mg in 1 g |

| Inactive Ingredients | |
|---|---|
| **Ingredient Name** | **Strength** |

| | |
|---|---|
| **CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)** (UNII: 809Y72KV36) | |
| **CARBOMER HOMOPOLYMER TYPE A (ALLYL PENTAERYTHRITOL CROSSLINKED)** (UNII: F68VH75CJC) | |
| **DIETHYL SEBACATE** (UNII: I41B9FJK6V) | |
| **EDETATE DISODIUM** (UNII: 7FLD91C86K) | |
| **LIGHT MINERAL OIL** (UNII: N6K5787QVP) | |
| **METHYLPARABEN** (UNII: A2I8C7HI9T) | |
| **PROPYLPARABEN** (UNII: Z8IX2SC1OH) | |
| **WATER** (UNII: 059QF0KO0R) | |
| **SODIUM HYDROXIDE** (UNII: 55X04QC32I) | |
| **SORBITAN MONOOLEATE** (UNII: 06XEA2VD56) | |
| **SORBITOL** (UNII: 506T60A25R) | |

## Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|---|---|---|---|
| **1** | NDC:0187-0653-01 | 1 in 1 CARTON | 04/25/2019 | |
| **1** | | 100 g in 1 TUBE; Type 0: Not a Combination Product | | |
| **2** | NDC:0187-0653-03 | 6 in 1 CARTON | 04/25/2019 | |
| **2** | | 3 g in 1 TUBE; Type 0: Not a Combination Product | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA209354 | 04/25/2019 | |

## Labeler - Bausch Health US, LLC (831922468)

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| Bausch Health Companies Inc. | | 245141858 | MANUFACTURE(0187-0653) , PACK(0187-0653) |

Revised: 1/2020 Bausch Health US, LLC