ALTRENO is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

**DOSAGE AND ADMINISTRATION**

- Apply a thin layer of ALTRENO to affected areas once daily. Avoid eyes, mouth, paranasal creases, and mucous membranes.
- Not for ophthalmic, oral, or intravaginal use.

**ADVERSE REACTIONS**

- Skin Irritation: Dryness, pain, erythema, irritation, and exfoliation may occur with use of ALTRENO. (5.1)
- Ultraviolet Light and Environmental Exposure: Minimize exposure to sunlight and sunlamps. Use sunscreen and protective clothing when sun exposure cannot be avoided. (5.2)
- Fish Allergies: Use ALTRENO with caution if allergic to fish due to potential for allergenicity to fish protein. Advise patients to contact their healthcare provider if they develop pruritus or urticaria. (5.3)

**WARNINGS AND PRECAUTIONS**

- The most common adverse reactions occurring in ≥1% of subjects and greater than vehicle were dryness, pain, erythema, irritation, and exfoliation (all at the application site). (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: 11/2019
Tretinoin is all-trans-retinoic acid, also known as (all-E)-3,7-dimethyl-9-
(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. It is a member of the
retinoid class of compounds and a metabolite of vitamin A. Tretinoin has the following
chemical structure:

![Chemical Structure of Tretinoin]

Molecular Formula: C_{20}H_{28}O_{2}  
Molecular Weight: 300.44

Each gram of ALTRENO contains 0.5 mg (0.05%) of tretinoin in an opaque, pale yellow
lotion base consisting of benzyl alcohol, butylated hydroxytoluene, carborer copolymer
type B (Pemulen TR-1), carborer homopolymer type A (Carbolp 981), glycerin,
methylparaben, mineral oil, octoxynol-9, purified water, sodium hyaluronate, soluble
collagen and trolamine.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tretinoin is a metabolite of vitamin A that binds with high affinity to specific retinoic acid
receptors located in both the cytosol and nucleus.

Tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RARα, RARB, and RARD) which act to modify gene expression, subsequent protein synthesis,
and epithelial cell growth and differentiation. It has not been established whether the
clinical effects of tretinoin are mediated through activation of retinoic acid receptors,
other mechanisms, or both.

Although the exact mode of action of tretinoin in acne treatment is unknown,
current evidence suggests that topical tretinoin decreases cohesiveness of follicular
epithelial cells with decreased microcomedo formation. Additionally, tretinoin
stimulates mitotic activity and increased turnover of follicular epithelial cells causing
extrusion of the comedones.
12.2 Pharmacodynamics
The pharmacodynamics of ALTRENO in the treatment of acne vulgaris are unknown.

12.3 Pharmacokinetics
Plasma concentrations of tretinoin and its major metabolites (isotretinoin and 4-oxo-isotretinoin) were evaluated in 20 subjects in an open-label, randomized, pharmacokinetic study. Subjects aged 10 years to less than 17 years old with acne vulgaris applied approximately 3.5 g of ALTRENO to the skin of the entire face (excluding eyes and lips), neck, upper chest, upper back and shoulders once daily for 14 days. Single-dose pharmacokinetic (PK) characteristics were determined from samples drawn on Days 1 and 2 of dosing and steady-state PK characteristics were determined from samples drawn on Days 14 and 15 under maximal use conditions. The mean baseline corrected C_max and AUC_{0-24} of tretinoin and its metabolites after once daily application of ALTRENO for 14 days are shown below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean (±SD) C_max (ng/mL)</th>
<th>Mean (±SD) AUC_{0-24} (ng*h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretinoin</td>
<td>0.33 (0.33)</td>
<td>6.46 (5.15)</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>0.49 (0.66)</td>
<td>9.30 (9.95)</td>
</tr>
<tr>
<td>4-oxo-isotretinoin</td>
<td>0.57 (0.82)</td>
<td>14.51 (18.28)</td>
</tr>
</tbody>
</table>

The mean concentrations of tretinoin and its metabolites (isotretinoin and 4-oxo-isotretinoin) remain relatively stable and unchanged over the 24-hour period after both the Day 1 dose and the Day 14 dose. Systemic concentrations of tretinoin appear to be at or near steady state by Day 14. Mean accumulation ratios of the baseline corrected AUC between Day 14 and Day 1 were 1.5, 4.5 and 7.3 for tretinoin, isotretinoin, and 4-oxo-isotretinoin, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
A 2-year dermal mouse carcinogenicity study was conducted with topical administration of 0.005%, 0.025% and 0.05% of a tretinoin gel formulation. Although no drug-related tumors were observed in surviving animals, the irritating nature of the drug product precluded daily dosing, confounding data interpretation and reducing the biological significance of these results.

Studies in hairless albino mice with a different formulation suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect was confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The genotoxic potential of tretinoin was evaluated in an in vitro bacterial reversion test, an in vitro chromosomal aberration assay in human lymphocytes and an in vivo rat micronucleus assay. All tests were negative.

In dermal fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (approximately 2 times the MRHD based on BSA comparison and assuming 100% absorption), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day and above (approximately the MRHD based on BSA comparison and assuming 100% absorption) were observed.

14 CLINICAL STUDIES
The safety and efficacy of once daily use of ALTRENO for the treatment of acne vulgaris were assessed in two multicenter, randomized, double-blind clinical trials enrolling 1640 subjects age 9 years and older with acne vulgaris. Enrolled subjects had a score of moderate (3) or severe (4) on the Evaluator’s Global Severity Score (EGSS). 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 non-inflammatory lesions (open and closed comedones) and two or fewer facial nodules. The coprimary efficacy endpoints of success on the EGSS, absolute change in noninflammatory lesion count, and absolute change in inflammatory lesion count were assessed at Week 12. Success on the EGSS was defined as at least a 2-grade improvement from Baseline and an EGSS score of clear (0) or almost clear (1). Table 3 lists the efficacy results for trials 1 (NCT02491060) and 2 (NCT02535871).

### Table 3: Efficacy Results at Week 12

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>ALTRENO (N=406)</th>
<th>Vehicle (N=414)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGSS: Clear or Almost Clear and 2-Grade Reduction from Baseline</td>
<td>16.5%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Non-Inflammatory Facial Lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Absolute Reduction</td>
<td>17.8</td>
<td>10.6</td>
</tr>
<tr>
<td>Mean Percent Reduction</td>
<td>47.5%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Inflammatory Facial Lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Absolute Reduction</td>
<td>13.1</td>
<td>10.2</td>
</tr>
<tr>
<td>Mean Percent Reduction</td>
<td>50.9%</td>
<td>40.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial 2</th>
<th>ALTRENO (N=413)</th>
<th>Vehicle (N=407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGSS: Clear or Almost Clear and 2-Grade Reduction from Baseline</td>
<td>19.8%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Non-Inflammatory Facial Lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Absolute Reduction</td>
<td>21.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Mean Percent Reduction</td>
<td>45.6%</td>
<td>31.9%</td>
</tr>
<tr>
<td>Inflammatory Facial Lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Absolute Reduction</td>
<td>13.9</td>
<td>10.7</td>
</tr>
<tr>
<td>Mean Percent Reduction</td>
<td>53.4%</td>
<td>41.5%</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING
ALTRENO (tretinoin) lotion, 0.05% is an opaque, pale yellow topical lotion and available as:
• 50 g pump (NDC 0187-0005-50)
• 20 g tube (NDC 0187-0005-20)
• 45 g tube (NDC 0187-0005-45)

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.

Store pump upright.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).
• Warn patients of the potential for skin irritation during treatment.
• Advise patients to minimize exposure to sunlight and sunlamp products and protective apparel (e.g., hat) when sun exposure cannot be avoided.

Manufactured for:
Bausch Health Americas, Inc.
Bridgewater, NJ 08807 USA

By:
Bausch Health Companies Inc.
Laval, Quebec H7L 4A8, Canada

U.S. Patent Number: 6,517,847
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9650302
## PATIENT INFORMATION

**ALTRENO™** (al-TREN-oh)  
(tretinoin) lotion, 0.05% for topical use

### Important information:
ALTRENO is for use on skin only. Do not use ALTRENO in your eyes, mouth, the corners of your nose, or vagina.

### What is ALTRENO?
ALTRENO is a prescription medicine used on the skin (topical) to treat people with acne. Acne is a condition in which the skin has blackheads, whiteheads, and other pimples.

It is not known if ALTRENO is safe and effective in children under 9 years of age.

### Before using ALTRENO, tell your healthcare provider about all your medical conditions, including if you:
- are allergic to fish. ALTRENO contains fish proteins. Tell your healthcare provider if you get hives or itching while using ALTRENO.
- have eczema or any other skin problems.
- have a sunburn.
- are pregnant or plan to become pregnant. It is not known if ALTRENO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ALTRENO passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

### How should I use ALTRENO?
- Use ALTRENO exactly as your healthcare provider tells you to use it.
- Apply a thin layer of ALTRENO to cover the affected areas 1 time each day.

**Applying ALTRENO:**
- ALTRENO comes in a tube and a pump. If you have been prescribed the:
  - **Tube:** Squeeze the lotion from the tube onto a fingertip. Apply a thin layer to cover the affected areas, as prescribed by your doctor. Spread ALTRENO evenly over the affected areas.
  - **Pump:** Fully depress the pump to dispense ALTRENO onto a fingertip. Apply a thin layer to cover the affected areas, as prescribed by your doctor. Spread ALTRENO evenly over the affected areas.
- Wash your hands after applying ALTRENO.

### What should I avoid while using ALTRENO?
- You should avoid sunlamps, tanning beds, and ultraviolet light during treatment with ALTRENO.
- Minimize exposure to sunlight.
- If you have to be in the sunlight or are sensitive to sunlight, use a sunscreen with an SPF (sun protection factor) of 15 or more and wear protective clothing and a wide-brimmed hat to cover the treated areas.

### What are the possible side effects of ALTRENO?
ALTRENO may cause serious side effects, including:

**Skin irritation.** ALTRENO may cause irritation including skin dryness, pain, redness, excessive flaking or peeling. If you develop these symptoms, your healthcare provider may tell you to use a moisturizer, decrease the number of times you apply ALTRENO, or completely stop treatment with ALTRENO. Avoid applying ALTRENO to skin that is affected by eczema or sunburned skin.

These are not all the possible side effects of ALTRENO. 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 ALTRENO?
- Store ALTRENO at room temperature between 68° to 77°F (20° to 25°C).
- Do not freeze.
- Store ALTRENO pump upright.

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

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

### What are the ingredients in ALTRENO?

**Active ingredient:** tretinoin

**Inactive ingredients:** benzyl alcohol, butylated hydroxytoluene, carbomer copolymer type B (Pemulen TR-1), carbomer homopolymer type A (Carbopol 981), glycerin, methylparaben, mineral oil, octoxynol-9, purified water, sodium hyaluronate, soluble collagen and trolamine.

**Manufactured for:** Bausch Health Americas, Inc., Bridgewater, NJ 08807 USA

**By:** Bausch Health Companies Inc., Laval, Quebec H7L 4A8, Canada

For more information, call 1-800-321-4576.

U.S. Patent Number: 6,517,847

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

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