Each gram of EPIDUO gel contains 1 mg (0.1%) adapalene and 25 mg (2.5%) benzoyl peroxide.

**Adverse Reactions**

Most commonly reported adverse events (≥1%) in patients treated with EPIDUO gel were dry skin, contact dermatitis, application site irritation, and skin irritation.

To report SUSPECTED ADVERSE REACTIONS, contact:

Goldera Laboratories, L.P. at 1-800-725-4127 or FDA at 1-888-FDA-1088 or www.fda.gov/medwatch

**Indications and Usage**

EPIDUO gel is a combination of adapalene (0.1%), benzoyl peroxide, and adapalene (0.1%) in patients aged 9 years and older.

**Dosage and Administration**

Apply a thin film of EPIDUO gel to affected areas of the face and/or trunk once daily after washing. Use a pea-sized amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips, and mucous membranes.

**Dosing Forms and Strengths**

Each gram of EPIDUO gel contains 1 mg (0.1%) adapalene and 25 mg (2.5%) benzoyl peroxide.

**Use In Specific Populations**

- **Pregnancy**
- **Nursing Mothers**
- **Pediatric Use**
- **Geriatric Use**

**Full Prescribing Information**

- **Indications and Usage**
- **Dosage and Administration**
- **Dosing Forms and Strengths**
- **Use In Specific Populations**

**Adverse Reactions**

Most commonly reported adverse events (≥1%) in patients treated with EPIDUO gel were dry skin, contact dermatitis, application site irritation, and skin irritation.

**Contraindications**

- **Local Cautions and Reactions**

**Warnings and Precautions**

- **Ultraviolet Light and Environmental Exposure**
- **Skin Irritation**

**Drug Interactions**

- **System Organ Class**
- **Dosage Form**
- **Preferred Term**

**Use In Specific Populations**

- **Pregnancy**
- **Nursing Mothers**
- **Pediatric Use**
- **Geriatric Use**

**Full Prescribing Information**

- **Indications and Usage**
- **Dosage and Administration**
- **Dosing Forms and Strengths**
- **Use In Specific Populations**

**Adverse Reactions**

Most commonly reported adverse events (≥1%) in patients treated with EPIDUO gel were dry skin, contact dermatitis, application site irritation, and skin irritation.
Benzoyl Peroxide:

Molecular formula: C14H12O
Molecular weight: 242.23
EPIDUO gel contains the following inactive ingredients: acrylamide/sodium acryloyldimethyltaurate copolymer, disodium edetate, docusate sodium, purified water, and sorbitan oleate.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Adapalene
Adapalene binds to specific retinoid acid nuclear receptors but does not bind to cytosolic receptor protein. Biochemical and pharmacological profile studies have demonstrated that adapalene is a ligand for the retinoid X receptor, a nuclear receptor involved in the differentiation, keratinization and inflammatory processes. However, the significance of these findings with regard to the mechanism of action of adapalene for the treatment of acne is unknown.

Benzoyl peroxide
Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects.

12.2 Pharmacokinetics
Pharmacodynamics of EPIDUO gel is unknown.

12.3 Toxicokinetics
A pharmacokinetic study was conducted in 10 adult subjects with acne vulgaris who were treated once daily for 30 days with 2 grams/day of EPIDUO gel applied to 1000 cm² of acne-involved skin, (face, chest, and upper back).

Two subjects (20%) had quantifiable adapalene plasma concentrations above the limit of quantification (LOQ = 0.1 ng/mL). The highest adapalene C₀ and AUC₀-∞ was 0.21 ng/mL and 1.99 ng·h/mL, respectively.

Excretion of adapalene appears to be primarily by the biliary route. Pharmacokinetics of EPIDUO gel in pediatric subjects have not been evaluated.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity, phototranscarcinogenicity, genotoxicity, or fertility studies were conducted with EPIDUO gel.

Carcinogenicity studies with adapalene have been conducted in mice at top doses of 0.4, 1.2, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m²/day). In terms of body surface area, the highest dose levels are 9.8 mg/m²/day (rats) and 7.4 mg/m²/day (mice) of the MRHD of 2 grams of EPIDUO gel. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed. No significant increase in tumor formation was observed in rodents topically treated with 15–25% benzoyl peroxide carbopol gel (1–10 times the concentration of benzoyl peroxide in EPIDUO gel) for two years. Rats received maximum daily applications of 1.8 times (males) and 205 (females) mg benzoyl peroxide/kg. In terms of body surface area, these doses are 27–40 times the MRHD. Similar results were observed in mice topically treated with 25% benzoyl peroxide carbopol gel for 56 weeks followed the intermediate treatment with 15% benzoyl peroxide carbopol gel for the rest of the 2 year study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years.

The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. However, the significance of this finding in humans is unknown.

In a photocarcinogenicity study conducted with 5% benzoyl peroxide carbopol gel, no increase in UV-induced tumor formation was observed in hairless mice topically treated for 40 weeks.

No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects in vitro (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or in vivo (mouse micronucleus test). Bacterial mutagenicity assays (Ames test) with benzoyl peroxide has provided mixed results, mutagenic potential was observed in a few but not in a majority of investigations. Benzoyl peroxide has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epididymal cells. It has also caused DNA-protein cross-links in the human cells, and has also induced a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells.

In rat oral studies, 20 mg adapalene/kg/day (120 mg/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F₁ males and females, or growth, development and reproductive function of F₁ offspring.

No fertility studies were conducted with benzoyl peroxide.

14 CLINICAL STUDIES
The safety and efficacy of EPIDUO gel applied once daily for the treatment of acne vulgaris were assessed in two 12-week, multicenter, controlled clinical studies of similar design, comparing EPIDUO gel to the gel vehicle in acne subjects. Treatment response was defined as the percent of subjects who had a two grade improvement in ‘Darier’ and ‘Almost Clear’ at Week 12 based on the Investigator’s Global Assessment (IGA) and mean absolute change from baseline at Week 12 in both inflammatory and non-inflammatory lesion counts. An IGA score of ‘Clear’ corresponded to very few scattered comedones and a few small papules. In Study 1, 517 subjects were randomized to EPIDUO gel, adapalene 0.1% in vehicle gel, benzoyl peroxide 2.5% in vehicle gel, or vehicle gel. The median age of these 517 subjects was 15 years old and 66% were males. At baseline subjects had between 20 to 50 inflammatory lesions and 30 to 100 non-inflammatory lesions. The majority of subjects had a baseline IGA score of ‘Moderate’ which corresponded to more than half of the face is involved, many comedones, papules and pustules. The efficacy results at week 12 are presented in Table 3. In Study 2, 1688 subjects were randomized to EPIDUO gel, adapalene 0.1% in vehicle gel, benzoyl peroxide 2.5% in vehicle gel, or vehicle gel. The median age of subjects was 16 years old and 49% were males. At baseline subjects had between 20 to 50 inflammatory lesions and 30 to 100 non-inflammatory lesions as well as an Investigator Global Assessment score of ‘Moderate’. The efficacy results at week 12 are presented in Table 3. In Study 3, 2856 subjects 9 to 11 years of age were randomized to EPIDUO gel or vehicle gel. The median age of subjects was 11 years and 24% were males. At baseline, subjects had a minimum of 50 but not more than 100 total lesions (inflammatory and/or non-inflammatory) with an Investigator Global Assessment score of ‘Moderate’. The efficacy results at week 12 are presented in Table 3.

<table>
<thead>
<tr>
<th>Study</th>
<th>Adapalene 0.1% in Vehicle gel</th>
<th>Benzoyl Peroxide 2.5% in Vehicle gel</th>
<th>Vehicle gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGA</td>
<td>G dv. Improvement and Clear</td>
<td>Almost Clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 (30%)</td>
<td>100 (25%)</td>
<td>92 (22%)</td>
</tr>
<tr>
<td></td>
<td>(30%)</td>
<td>(25%)</td>
<td>(22%)</td>
</tr>
<tr>
<td>Inflammatory Lesions: Mean Absolute (Percent) Change</td>
<td>15.4 (53%)</td>
<td>12.3 (41.7%)</td>
<td>13.7 (47.6%)</td>
</tr>
<tr>
<td></td>
<td>(53%)</td>
<td>(41.7%)</td>
<td>(47.6%)</td>
</tr>
<tr>
<td>Non-inflammatory Lesions: Mean Absolute (Percent) Change</td>
<td>24.6 (48.1%)</td>
<td>21.0 (40.8%)</td>
<td>19.2 (37.2%)</td>
</tr>
<tr>
<td></td>
<td>(48.1%)</td>
<td>(40.8%)</td>
<td>(37.2%)</td>
</tr>
</tbody>
</table>

In both Studies 1 and 2 the treatment effect was smaller in subjects with a small number of baseline lesions than in subjects with a large number of baseline lesions.

### 16 HOW SUPPLIED/STORAGE AND HANDLING
EPIDUO (adapalene and benzoyl peroxide) gel 0.1% / 2.5% is white to very pale yellow in color and opaque in appearance, and is supplied as follows:

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 gram tube</td>
<td>NDC 0099-9000-45</td>
</tr>
<tr>
<td>45 gram pump</td>
<td>NDC 0099-5958-25</td>
</tr>
</tbody>
</table>

### 17 PATIENT COUNSELING INFORMATION
See FDA Approved Patient Labeling (Patient Information)

Information for Patients
- Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply EPIDUO gel as a thin layer, avoiding the eyes, lips and mucous membranes.
- Advise patients not to use more than the recommended amount and not to apply more than once per day as this will not produce faster results, but may increase irritation.
- EPIDUO gel may cause irritation such as erythema, scaling, dryness, stinging or burning.
- Advise patients to minimize exposure to sunlight, including sunlamps. Recommend the use of sunscreen products and protective apparel, (e.g., hat) when exposure cannot be avoided.