Summary of Product Characteristics

1. Name of the medicinal product

Adaferin Gel

2. Qualitative and quantitative composition

Adapalene 0.1% w/w
1g gel contains 1mg adapalene

Excipients with known effect:
Propylene glycol
Methyl parahydroxybenzoate
For the full list of excipients, see section 6.1

3. Pharmaceutical form

Topical Gel
A smooth white gel

4. Clinical particulars

4.1 Therapeutic indications

Continuous treatment of acne vulgaris where papules and postules predominate.
Acne of the chest, face or back is appropriate for treatment.

4.2 Posology and method of administration

Adaferin Gel should be applied to the acne affected areas once a day before retiring and after washing. A thin film of gel should be applied, with the fingertips, avoiding the eyes and lips (see 4.4 Special Warnings and Special Precautions for Use, below).
Ensure that the affected areas are dry before application.
Since it is customary to alternate therapies in the treatment of acne, it is recommended that the physician assess the continued improvement of the patient after three months of treatment with Adaferin Gel.
With patients for whom it is necessary to reduce the frequency of application or to temporarily discontinue treatment, frequency of application may be restored or therapy resumed once it is judged that the patient can again tolerate the treatment.
If patients use cosmetics, these should be non-comedogenic and non-astringent.
Paediatric population: The safety and effectiveness of Adaferin Gel have not been studied in children below 12 years of age.
Adaferin gel should not be used in patients with severe acne.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

If a reaction suggesting sensitivity or severe irritation occurs, use of the medication should be discontinued. If the degree of local irritation warrants, patients should be directed to use the medication less frequently, to discontinue use temporarily, or to discontinue use altogether.
Adaferin Gel should not come into contact with the eyes, mouth, nostrils or mucous membranes.
If product enters the eye, wash immediately with warm water. The product should not be applied to either broken (cut and abrasions) or eczematous skin, nor should it be used in patients with severe acne involving large areas of the body.
The excipient propylene glycol may cause skin irritation and methyl parahydroxybenzoate may cause allergic reactions which can possibly be delayed.

4.5 Interaction with other medicinal products and other forms of interaction

There are no known interactions with other medications which might be used cutaneously and concurrently with Adaferin Gel, however, other retinoids or drugs with a similar mode of action should not be used concurrently with adapalene.
Adapalene is essentially stable to oxygen and light and is chemically non-reactive. Whilst extensive studies in animals and man have shown neither phototoxic nor photoallergic potential for adapalene, the safety of using adapalene during repeated exposure to sunlight or UV irradiation has not been established in either animals or man. Exposure to excessive sunlight or UV irradiation should be avoided.
Absorption of adapalene through human skin is low (see 5.2 Pharmacokinetic Properties) and therefore interaction with systemic medications is unlikely. There is no evidence that the efficacy of oral drugs such as contraceptives and antibiotics is influenced by the cutaneous use of Adaferin Gel.
Adaferin Gel has a potential for mild local irritation, and therefore it is possible that concomitant use of peeling agents, abrasive cleansers, strong drying agents, astringents or irritant products (aromatic and alcoholic agents) may produce additive irritant effects. However, cutaneous antiacne treatment (eg erythromycin up to 4%) or clindamycin phosphate (1% as the base) solutions or benzoyl peroxide water based gels up to 10% may be used in the morning when Adaferin Gel is used at night as there is no mutual degradation or cumulative irritation.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Animal studies by the oral route have shown reproductive toxicity at high systemic exposure (see section 5.3). Clinical experience with locally applied adapalene in pregnancy is limited but the few available data do not indicate harmful effects on pregnancy or on the health of the foetus exposed in early pregnancy. Due to the limited available data and because a very weak cutaneous passage of adapalene is possible, Adaferin should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued.

Breast-feeding:

No study on animal or human milk transfer was conducted after cutaneous application of Adaferin . No effects on the suckling child are anticipated since the systemic exposure of the breast-feeding woman to Adaferin is negligible.
Adaferin can be used during breastfeeding. To avoid contact exposure of the infant, application of Adaferin to the chest should be avoided when used during breast-feeding.

4.7 Effects on ability to drive and use machines

Adaferin Gel has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adaferin may cause the following adverse drug reactions:

Body System (MeDRA)	Frequency	Adverse Drug Reaction
Skin and subcutaneous tissue disorders	Common (≥1/100 to <1/10)	Dry skin, skin irritation, skin burning sensation, erythema
	Uncommon (≥1/1000 to <1/100)	Dermatitis contact, skin discomfort, sunburn, pruritus, skin exfoliation, acne
	Unknown*	Pain of skin, skin swelling, eyelid irritation, eyelid erythema, eyelid pruritus, eyelid swelling

*Post marketing surveillance data

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Adaferin Gel is not to be taken orally and is for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur.
The acute oral dose of Adaferin Gel required to produce toxic effects in mice is greater that 10 mg/kg. Nevertheless, unless the amount accidentally ingested is small, an appropriate method of gastric emptying should be considered.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: D10A Anti-Acne Preparations for Topical Use
ATC code: D10AD03
Adapalene is a retinoid-like compound which in, in vivo and in vitro models of inflammation, has been demonstrated to possess anti-inflammatory properties. Adapalene is essentially stable to oxygen and light and is chemically non-reactive. Mechanically,
adapalene binds like tretinoin to specific retinoic acid nuclear receptors but, unlike tretinoin not to cytosolic receptor binding proteins.
Adapalene applied cutaneously is comedolytic in the rhino mouse model and also has effects on the abnormal processes of epidermal keratinization and differentiation, both of which are present in the pathogenesis of acne vulgaris. The mode of action of adapalene is suggested to be a normalisation of differentiation of follicular epithelial cells resulting in decreased microcomedone formation.
Adapalene is superior to reference retinoids in standard anti-inflammatory assays, both in vivo and in vitro. Mechanistically, it inhibits chemotactic and chemokinetic responses of human polymorphonuclear leucocytes and also the metabolism by lipoxidation of arachidonic acid to pro-inflammatory mediators. This profile suggests that the cell mediated inflammatory component of acne may be modified by adapalene.

5.2 Pharmacokinetic properties

Absorption of adapalene through human skin is low, in clinical trial measurable plasma adapalene levels where not found following chronic cutaneous application to large areas of acneic skin with an analytical sensitivity of 0.15 ng/ml.
After administration of [14C] adapalene in rats (IV, IP, oral and cutaneous), rabbits (IV, oral and cutaneous) and dogs (IV and oral), radioactivity was distributed in several tissues, the highest levels being found in liver, spleen, adrenals and ovaries.
Metabolism in animals has been tentatively identified as being mainly by O-demethylation, hydroxylation and conjugation, and excretion is primarily by the biliary route.

5.3 Preclinical safety data

In animal studies, adapalene was well tolerated on cutaneous application for periods of up to six months in rabbits and for up to two years in mice. The major symptom of toxicity found in all animal species by the oral route were related to a hypervitaminosis A syndrome, and included bone dissolution, elevated alkaline phosphatase and a slight anaemia. Large oral doses of adapalene produced no adverse neurological, caridovascular or respiratory effects in animals. Adapalene is not mutagenic. Lifetime studies with adapalene have been completed in mice at cutaneous doses of 0.6,2 and 6 mg/kg/day and in rats at oral doses of 0.15, 0.5 and 1.5 mg/kg/day. The only significant finding was a statistically significant increase of benign phaeochromocytomas of the adrenal medulla among male rats receiving adapalene at 1.5 mg/kg/day. These changes are unlikely to be of relevance to the
cutaneous use of adapalene.
Adapalene produces teratogenic effects by the oral route in rats and rabbits. At cutaneous doses up to 200-fold the therapeutic dose, producing circulating plasma levels of adapalene

at least 35 to 120 times higher than plasma levels demonstrated in therapeutic use, adapalene increased the incidence of additional ribs in rats and rabbits, without increasing the incidence of major malformations.
It is not known whether adapalene is secreted in animal or human milk. In animal studies, infant rats suckled by mother with circulating levels of adapalene at least 300 times those demonstrated in clinical use developed normally.

6. Pharmaceutical particulars

6.1 List of excipients

Carbomer 980

Propylene Glycol

Poloxamer 182

Disodium Edetate

Methyl Parahydroxybenzoate

Phenoxyethanol

Sodium Hydroxide or HCL
Purified Water

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years
After first opening, the Gel should be used within 6 months.

6.4 Special precautions for storage
Store below 25ºC.
Keep out of the sight and reach of children

6.5 Nature and contents of container
White LDPE tube with white PP screw cap. Pack size 30g.

6.6 Special precautions for disposal and other handling
A thin film of the gel should be applied, avoiding eyes, lips and mucous membranes.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. **Manufacturer:** Laboratories GALDERMA, France

8. Registration holder:

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.
Registration number:1285029165

The format of this leaflet was determined by the Ministry of Health that checked and approved its content in December 2013.