1. NAME OF THE MEDICINAL PRODUCT

Adapaleen/ Benzoylperoxide Galen 1 mg/g + 25 mg/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains:
adapalene 1 mg (0.1% w/w)
benzoyl peroxide, hydrous, equivalent to 25 mg (2.5% w/w) of anhydrous benzoyl peroxide

Excipient(s) with known effect:
Propylene glycol (E1520) 40 mg/g (4.00% w/w) and 3 mg/g (0.3% w/w) polysorbates.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.
Homogeneous opaque gel of white to very pale-yellow colour

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is indicated for cutaneous treatment of Acne vulgaris when comedones, papules and pustules are present (see section 5.1).

Adapaleen/ Benzoylperoxide Galen is indicated in adults, adolescents and children aged 9 years and above.

4.2 Posology and method of administration

Gel should be applied to the entire acne affected areas once a day in the evening on a clean and dry skin. A thin film of gel should be applied, with the fingertips, avoiding the eyes and lips (see section 4.4).

If irritation occurs, the patient should be directed to apply non-comedogenic moisturizers, to use the medication less frequently (e.g. every other day), to suspend use temporarily, or to discontinue use altogether.

The duration of treatment should be determined by the Doctor on the basis of the clinical condition. Early signs of clinical improvement usually appear after 1 to 4 weeks of treatment.

The safety and effectiveness of adapalene/benzoyl peroxide have not been studied in children below 9 years of age.

Method of administration
Cutaneous use only.

Patients should be instructed to wash their hands after applying the medicinal product.

4.3 Contraindications

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

- Pregnancy (see section 4.6)
- Women planning a pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

Adapaleen/ Benzoylperoxide Galen should not be applied to damaged skin, either broken (cuts or abrasions), eczematous or sunburned.

Adapaleen/ Benzoylperoxide Galen should not come into contact with the eyes, mouth, nostrils or mucous membranes. If product enters the eye, it should be washed immediately with warm water.

If a reaction suggesting sensitivity to any component of the formula occurs, the use of this medicinal product should be discontinued.

Excessive exposure to sunlight or UV radiation should be avoided.

Adapaleen/ Benzoylperoxide Galen should not come into contact with any coloured material including hair and dyed fabrics as this may result in bleaching and discoloration.

This product contains 40 mg of propylene glycol (E1520) in each gram of gel which is equivalent to 4.00% w/w that may cause skin irritation.

This product contains polysorbates which can cause allergic reactions.

This medicine can contain up to 2.5 mg of benzoic acid per g of gel, as degradation product of benzoyl peroxide. Benzoic acid may cause local irritation.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

From previous experience with adapalene and benzoyl peroxide, there are no known interactions with other medicinal products which might be used cutaneously and concurrently with the gel. However, other retinoids or benzoyl peroxide or medicinal products with a similar mode of action should not be used concurrently. Caution should be exercised if cosmetics with desquamative, irritant or drying effects are used, as they may produce additive irritant effects with this medicinal product.

Absorption of adapalene through human skin is low (see section 5.2), and therefore interaction with systemic medicinal products is unlikely.

The percutaneous penetration of benzoyl peroxide in the skin is low and the drug substance is completely metabolised into benzoic acid which is rapidly eliminated. Therefore, the potential interaction of benzoic acid with systemic medicinal products is unlikely to occur.

4.6 Fertility, pregnancy and lactation

Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

<u>Pregnancy</u>
Adapalene/ benzoyl peroxide is contraindicated in pregnancy or in women planning a pregnancy (see section 4.3).

There are no or limited amount of data from the use of adapalene topically in pregnant women.

Animal studies by the oral route have shown reproductive toxicity at high systemic exposure (see section 5.3).

Clinical experience with locally applied adapalene and benzoyl peroxide in pregnancy is limited.

If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

Breast-feeding
No study on animal or human milk transfer was conducted after cutaneous application of adapalene and benzoyl peroxide gel.

No effects on the suckling child are anticipated since the systemic exposure of the breast-feeding woman to this medicinal product is negligible. Adapaleen/ Benzoylperoxide Galen can be used during breast-feeding.

To avoid contact exposure of the infant, application of this gel to the chest should be avoided when used during breast-feeding.

Fertility
No human fertility studies were conducted with adapalene and benzoyl peroxide gel.

However, no effects of adapalene or benzoyl peroxide on fertility were found in rats in reproductive studies (See section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adapaleen/ Benzoylperoxide Galen may cause the following adverse reactions at the site of application:

MedDRA System Organ Class	**Frequency**	**Adverse drug reaction**
Eye disorders	Not known (cannot be estimated from the available data)*	Eyelid oedema
Immune system disorders	Not known (cannot be estimated from the available data)*	Anaphylactic reaction
Respiratory, thoracic, and mediastinal disorders	Not known (cannot be estimated from the available data)*	Throat tightness, dyspnoea
Skin and subcutaneous tissue disorders	Common (≥1/100 to <1/10)	Dry skin, irritative contact dermatitis, skin irritation, skin burning sensation, erythema, skin exfoliation (scaling)
	Uncommon (≥1/1 000 to <1/100)	Pruritus, sunburn
	Not known (cannot be estimated from the available data)*	Allergic contact dermatitis, swelling face, pain of skin (stinging pain), blisters (vesicles), skin discolouration (hyperpigmentation and hypopigmentation), urticaria, application site burn**

*Post marketing surveillance data

**Most of the cases of "application site burn" were superficial burns but cases with second degree burn or severe burn reactions have been reported.

If skin irritation appears after application of this medicinal product, the intensity is generally mild or moderate, with local tolerability signs and symptoms (erythema, dryness, scaling, burning and pain of skin (stinging pain) peaking during the first week and then subsiding spontaneously.

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 via the national reporting system listed in Appendix V.

4.9 Overdose

Adapaleen/ Benzoylperoxide Galen is for once-daily cutaneous use only.

In case of accidental ingestion, appropriate symptomatic measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Acne preparations for topical use, Retinoids for topical use in acne
ATC code:D10AD53

Mechanism of action and Pharmacodynamic effects
Adapaleen/ Benzoylperoxide Galen combines two active substances, which act through different, but complementary, mechanisms of action:

- *Adapalene:* Adapalene is a chemically stable, naphthoic acid derivative with retinoid-like activity. Biochemical and pharmacological profile studies have demonstrated that adapalene acts in the pathology of *Acne vulgaris:* it is a potent modulator of cellular differentiation and keratinisation and it has anti-inflammatory properties. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors. Current evidence suggests that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Adapalene inhibits the chemotactic (directional) and chemokinetic (random) responses of human polymorphonuclear leucocytes in *in vitro* assay models; it also inhibits the metabolism of arachidonic acid to inflammatory mediators. *In vitro* studies have shown inhibition of the AP-1 factors and the inhibition of the expression of toll like receptors 2. This profile suggests that the cell mediated inflammatory component of acne is reduced by adapalene.

- *Benzoyl peroxide:* Benzoyl peroxide has been shown to have antimicrobial activity; particularly against *Cutibacterium acnes*, which is abnormally present in the acne-affected pilosebaceous unit. The mechanism of action of Benzoyl peroxide has been explained by its highly lipophilic activity, enabling its penetration through the epidermis into bacterial and keratinocyte cell membranes of the pilosebaceous unit. Benzoyl peroxide is recognized as a very effective broad-spectrum antibacterial agent in the treatment of acne vulgaris. It has been demonstrated to exert bactericidal effect by generating free radicals that oxidize proteins and other essential cellular components in the bacterium wall. The minimum inhibitory concentration of benzoyl peroxide is bactericidal and has demonstrated effectiveness on antibiotic-sensitive and antibiotic-resistant *C. acnes* strains. Additionally, benzoyl peroxide has demonstrated exfoliative and keratolytic activities.

Clinical efficacy of adapalene/benzoyl peroxide in patients aged 12 years and older

The safety and efficacy of adapalene/benzoyl peroxide gel applied once daily for the treatment of Acne vulgaris were assessed in two 12-week, multicenter, controlled clinical studies of similar design, comparing adapalene/benzoyl peroxide gel to its individual active components and to the gel vehicle in acne patients. A total of 2 185 patients were enrolled in Study 1 and Study 2. The distribution of patients in the two studies was approximately 49% male and 51% female, 12 years of age or older (mean age: 18.3 years; range 12-50), presenting 20 to 50 inflammatory lesions and 30 to 100 noninflammatory lesions at baseline. The patients treated the face and other acne affected areas as needed once daily in the evening.

The efficacy criteria were:

- Success rate, percentage of patients rated 'Clear' and 'Almost Clear' at Week 12 based on the Investigator's Global Assessment (IGA);
- Change and Percent Change from baseline at Week 12 in: Inflammatory lesion counts; Non-inflammatory lesion counts; Total lesion count

The efficacy results are presented for each study in Table 1 and combined results in Table 2. Adapalene/benzoyl peroxide gel was shown to be more effective compared to its monads and gel vehicle in both studies. Overall, the net beneficial effect (active minus vehicle) obtained from adapalene/benzoyl peroxide gel was greater than the sum of the net benefits obtained from the individual components, thus indicating a potentiation of the therapeutic activities of these substances when used in a fixed-dose combination. An early treatment effect of adapalene/benzoyl peroxide gel was consistently observed in Study 1 and Study 2 for Inflammatory Lesions at Week 1 of treatment. Noninflammatory lesions (open and closed comedones) noticeably responded between the first and fourth week of treatment. The benefit on nodules in acne has not been established.

Table 1: Clinical efficacy in two comparative trials

Study 1				
Study 1 Week 12 LOCF; ITT	**Adapalene+BPO N=149**	**Adapalene N=148**	**BPO N=149**	**Vehicle N=71**
Success (Clear, Almost Clear)	41 (27.5%)	23 (15.5%) p=0.008	23 (15.4%) p=0.003	7 (9.9%) p=0.002
Median Reduction (% Reduction) in				
Inflammatory Lesion Count	17 (62.8%)	13 (45.7%) p<0.001	13 (43.6%) p<0.001	11 (37.8%) p<0.001
Noninflammatory Lesion Count	22 (51.2%)	17 (33.3%) p<0.001	16 (36.4%) p<0.001	14 (37.5%) p<0.001
Total lesion Count	40 (51.0%)	29 (35.4%) p<0.001	27 (35.6%) p<0.001	26 (31.0%) p<0.001
Study 2				
Study 2 Week 12 LOCF; ITT	**Adapalene+BPO N=415**	**Adapalene N=420**	**BPO N=415**	**Vehicle N=418**
Success (Clear, Almost Clear)	125 (30.1%)	83 (19.8%) p<0.001	92 (22.2%) p=0.006	47 (11.3%) p<0.001
Median Reduction (% Reduction) in				
Inflammatory Lesion Count	16 (62.1%)	14 (50.0%) p<0.001	16 (55.6%) p=0.068	10 (34.3%) p<0.001
Noninflammatory Lesion Count	24 (53.8%)	22 (49.1%) p=0.048	20 (44.1%) p<0.001	14 (29.5%) p<0.001

Total lesion Count	45 (56.3%)	39 (46.9%) p=0.002	38 (48.1%) p<0.001	24 (28.0%) p<0.001

Table 2: Clinical efficacy in combined comparative trials

	Adapalene+BPO N=564	**Adapalene N=568**	**BPO N=564**	**Vehicle N=489**
Success (Clear, Almost Clear)	166 (29.4%)	106 (18.7%)	115 (20.4%)	54 (11.1%)
Median Reduction (% Reduction) in:				
Inflammatory Lesion Count	16.0 (62.1)	14.0 (50.0)	15.0(54.0)	10.0 (35.0)
Noninflammatory Lesion Count	23.5 (52.8)	21.0 (45.0)	19.0 (42.5)	14.0 (30.7)
Total lesion Count	41.0 (54.8)	34.0 (44.0)	33.0 (44.9)	23.0 (29.1)

Clinical efficacy of adapalene/benzoyl peroxide in children 9 to 11 years old
During a paediatric clinical trial, 285 children with acne vulgaris, aged 9-11 years (53% of the subjects were 11 years old, 33% were 10 years old and 14% were 9 years old) with a score of 3 (moderate) on the IGA scale and a minimum of 20 but not more than 100 total lesions (Noninflammatory and/or Inflammatory) on the face (including the nose) at baseline were treated with adapalene/benzoyl peroxide gel once daily for 12 weeks.

The study concludes that the efficacy and safety profiles of adapalene/benzoyl peroxide gel in the treatment of facial acne in this specific younger age group are consistent with results of other pivotal studies in subjects with acne vulgaris aged 12 years and older showing significant efficacy with an acceptable tolerability. A sustained early treatment effect of adapalene/benzoyl peroxide gel compared to Gel Vehicle was consistently observed for all Lesions (Inflammatory, Non-Inflammatory, and Total) at Week 1 and continuing to Week 12.

Study 3		
Week 12 LOCF; ITT	**Adapalene+BPO N=142**	**Vehicle N=143**
Success (Clear, Almost Clear)	67 (47.2%)	22 (15.4%)
Median Reduction (% Reduction) in:		
Inflammatory Lesion Count	6 (62.5%)	1 (11.5%)
Noninflammatory Lesion Count	19 (67.6%)	5 (13.2%)
Total lesion Count	26 (66.9%)	8 (18.4%)

5.2 Pharmacokinetic properties

The pharmacokinetic (PK) properties of adapalene/benzoyl peroxide gel are similar to the PK profile of adapalene 0.1% gel alone.

In a 30-day clinical PK study, conducted in patients with acne who were tested with either the fixed-combination gel or with an adapalene 0.1% matched formula under maximized conditions (with application of 2 g gel per day), adapalene was not quantifiable in the majority of plasma samples (limit of quantification 0.1 ng/ml). Low levels of adapalene (C_{max} between 0.1 and 0.2 ng/ml) were measured in two blood samples taken from the subjects treated with adapalene/benzoyl peroxide gel and in three samples from the subjects treated with adapalene 0.1% gel. The highest adapalene AUC_{0-24h} determined in the fixed-combination group was 1.99 ng.h/ml.

These results are comparable to those obtained in previous clinical PK studies on various adapalene 0.1% formulations, where systemic exposure to adapalene was consistently low.

The percutaneous penetration of benzoyl peroxide is low; when applied on the skin, it is completely converted into benzoic acid which is rapidly eliminated.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, phototoxicity or carcinogenicity.

Reproductive toxicology studies with adapalene have been performed by the oral and dermal routes of administration in the rat and rabbit. A teratogenic effect has been demonstrated at high systemic exposures (oral doses from 25 mg/kg/day). At lower exposures (dermal dose of 6 mg/kg/day), changes in the numbers of ribs or vertebrae were seen.

Animal studies performed with adapalene/benzoyl peroxide gel include local tolerance studies and dermal repeat-dose toxicity studies in rat, dog and minipig up to 13 weeks and demonstrated local irritation and a potential for sensitization, as expected for a combination containing benzoyl peroxide. Systemic exposure to adapalene following repeat dermal application of the fixed combination in animals is very low, consistent with clinical pharmacokinetic data. Benzoyl peroxide is rapidly and completely converted to benzoic acid in the skin and after absorption is eliminated in the urine, with limited systemic exposure.

Reproductive toxicity of adapalene was tested by the oral route in rats for fertility.

There were no adverse effects upon reproductive performance and fertility, F1 litter survival, growth and development to weaning, and subsequent reproductive performance following treatment with adapalene oral at doses up to 20 mg/kg/day.

A reproductive and developmental toxicity study conducted in rats exposed groups to oral doses of benzoyl peroxide of up 1 000 mg/kg/day (5 mL/kg) showed that benzoyl peroxide did not induce teratogenicity or effects on reproductive function at doses up to 500 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol (E1520)
Glycerol
Sepineo P600
Poloxamer 124
Disodium edetate
Docusate sodium
Purified water

Sepineo P600 is a coprocessed excipient consisting of:
Acrylamide and sodium acryloyldimethyltaurate copolymer (1:1), isohexadecane, polysorbate 80, sorbitan oleate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months
In-use shelf life (after first opening): 6 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

White HDPE/LLDPE plastic tubes with a white HDPE head, having an aluminium peel-off seal and closed with a white polypropylene screw-cap.
One tube of 30 g
One tube of 45 g
One tube of 60 g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GALENpharma GmbH
Wittland 13
24109 Kiel
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 132008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 16 december 2024

10. DATE OF REVISION OF THE TEXT

Laatst gedeeltelijke wijziging betreft rubriek 6.3: 5 september 2025.