SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Adabencutan 3 mg/g + 25 mg/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains:
adapalene 3 mg (0.3% 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 4.2 and 5.1).
Adabencutan 3 mg/g + 25 mg/g gel is indicated in adults and adolescents aged 12 years and over.

4.2 Posology and method of administration

Gel should be applied to the entire acne affected areas of the face and the trunk once a day in the evening on a clean and dry skin.

The duration of treatment should be determined by the Doctor on the basis of the clinical condition and on the therapeutic response to the treatment. Early signs of clinical improvement usually appear after 1 to 4 weeks of treatment. If no improvement is observed after 4-8 weeks of treatment, the benefit of continued treatment should be reconsidered.

A lower strength of this gel is available (Adabencutan 1 mg/g + 25 mg/g gel) and this concentration should be considered in patients with moderate acne vulgaris (see section 5.1).

When the entire face is involved with numerous papulopustules, an increased clinical benefit was observed in the subjects treated with adapalene/ benzoyl peroxide 0.3%/2.5% gel compared with the reference therapy (adapalene/ benzoyl peroxide 1 mg/g + 25 mg/g gel). Physicians may choose between the two concentrations based on the presenting patient's clinical condition and severity.

Special populations
Elderly
The safety and efficacy of adapalene/ benzoyl peroxide gel in geriatric patients aged 65 years and above have not been established.

Renal and hepatic impairment
This medicinal product has not been studied in patients with renal and hepatic impairment.

Paediatric population
The safety and efficacy of this medicinal product have not been studied in children below 12 years of age.

Method of administration
Cutaneous use only.

Gel should be applied in thin layer on the affected areas of the face and/or trunk once daily after washing. It is recommended to use a pea-sized amount for each area of the face (e.g. forehead, chin, each cheek), avoiding the eyes and lips (see section 4.4).

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

Cosmetics may be applied after the medicinal product has dried.

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

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

Adabencutan 3 mg/g + 25 mg/g gel should not be applied to damaged skin, either broken (cuts or abrasions), eczematous or sunburned.

Adabencutan 3 mg/g + 25 mg/g gel 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.

Adabencutan 3 mg/g + 25 mg/g gel should not come into contact with any coloured material including hair and dyed fabrics as this may result in bleaching and discoloration.

The efficacy and safety of adapalene/benzoyl peroxide gel in patients with severe nodular or deep nodulocystic acne have not been studied. As patients with severe nodular / nodulocystic acne are at increased risk of permanent scarring secondary to acne lesions, the use of this gel in these patients is not recommended due to the risk of insufficient therapeutic response.

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.

Pregnancy

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. Available pharmacokinetic data in rats have shown excretion of adapalene in milk after oral or intravenous administration of adapalene.

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from this therapy weighting the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

Adabencutan 3 mg/g + 25 mg/g gel has no or negligible effects on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile
Approximately 10% of patients can be expected to experience adverse skin reactions. Treatment-related adverse reactions typically associated with use of adapalene/benzoyl peroxide gel include mild to moderate application site reactions, such as skin irritation mainly characterized by scaling, dryness, erythema, and burning/stinging. Recommendation is to use moisturiser, temporarily reduce the application frequency to every other day, or temporarily discontinue its use until once daily schedule can be resumed.

These reactions usually occur early in the treatment and tend to gradually decrease over time.

Tabulated summary of adverse reactions
The adverse reactions are classified by System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to 1<100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data) and were reported with adapalene/bezoyl peroxide gel in vehicle-controlled phase 3 clinical study (see Table 1).

Table 1: Adverse events

MedDRA System Organ Class	**Frequency**	**Adverse drug reaction**
Eye disorders	Uncommon	Erythema of eyelid
	Not known*	Eyelid oedema
Immune system disorders	Not known *	Anaphylactic reaction
Nervous system disorders	Uncommon	Paresthesia (tingling at application site)
Respiratory, thoracic and mediastinal disorders	Not known *	Throat tightness, dyspnoea
Skin and subcutaneous tissue disorders	Common	Atopic dermatitis, eczema, skin burning sensation, skin irritation, erythema, skin exfoliation (scaling)
	Uncommon	Dry skin, pruritus, rash
	Not known *	Allergic contact dermatitis, swelling face, pain of skin (stinging pain), blisters (vesicles), skin discoloration (hyperpigmentation and hypopigmentation), urticaria, application site burn**

*Post marketing surveillance data reported since the global launch of adapalene/benzoyl peroxide 0.1%/2.5% gel, from a population of unknown size
**Most of the cases of "application site burn" were superficial burns but cases with second degree burn or severe burn reactions have been reported.

Skin-related adverse events were more frequent with adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel than the lower concentration gel (adapalene 0.1% / benzoyl peroxide 2.5%) as compared to vehicle. In the pivotal study (see section 5.1), 9.2% of subjects in the combined population treated with adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel had skin-related adverse events and 3.7% in the population treated with adapalene/benzoyl peroxide gel compared to Vehicle gel group (2.9%).

In addition to some of the above, other adverse drug reactions were reported in clinical trials with adapalene 0.1% / benzoyl peroxide 2.5% gel, the previously approved fixed combination of adapalene and benzoyl peroxide:

- Other adverse drug reactions reported in clinical trials with adapalene/benzoyl peroxide gel are irritative contact dermatitis (common) and sunburn (uncommon).

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

Adabencutan 3 mg/g + 25 mg/g gel is for once-daily cutaneous use only. Excessive application of the gel may result in severe irritation. In this event, the patient must discontinue the treatment and wait until the skin has recovered.

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
Adabencutan 3 mg/g + 25 mg/g gel 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 keratinization, 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 and safety

The safety and efficacy of adapalene/benzoyl peroxide gel applied once daily for the treatment of Acne vulgaris were assessed in 12-week, multicenter, randomized, double-blind, controlled clinical controlled clinical study, comparing adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel to the gel vehicle in 503 acne patients. In this study, 217 patients were treated with adapalene/benzoyl peroxide 0.3%/2.5% gel, 217 patients with adapalene 0.1% / benzoyl peroxide 2.5% gel and 69 patients with the Vehicle gel.

The efficacy criteria were:

- Success rate, percentage of patients rated 'Clear' or 'Almost Clear' at Week 12 with at least a two-grade improvement based on the Investigator's Global Assessment (IGA). An IGA score of 'Clear' corresponded to clear skin with no inflammatory or noninflammatory lesions. An IGA score of 'Almost Clear' corresponded to a few scattered comedones and a few small papules.
- Mean absolute change from baseline at week 12 in both inflammatory and non-inflammatory lesion counts.

At Baseline, 50% of enrolled patients had acne severity assessed as "moderate" (IGA=3) and 50% had scores of "severe" (IGA=4). In the overall study population, up to two nodules were allowed. For lesion counts, subjects had an average of 98 total lesions (range: 51-226), of which the mean number of inflammatory lesions was 38 (range: 20-99) and the mean number of non-inflammatory lesions was 60 (range: 30-149). The age of the patients ranged from 12 to 57 years (mean age: 19.6 years), with 273 (54.3%) patients 12 to 17 years of age. A similar number of males (47.7%) and females (52.3%) were enrolled.

In this pivotal study, 55.2% of patients in the severe stratum had truncal acne. The patients treated the face and other acne affected areas on the trunk as needed once daily in the evening.

Statistical analyses were performed to compare and interpret study results in a stepwise manner:

- adapalene/benzoyl peroxide 0.3%/2.5% gel versus Vehicle gel in the overall population of patients with moderate and severe acne (IGA=3 and IGA=4).
- adapalene/benzoyl peroxide 0.3%/2.5% gel versus Vehicle gel in the subgroup of patients with severe acne (IGA=4).

The efficacy results are shown in Table 2 for the combined moderate and severe acne populations.

Table 2: Clinical efficacy in the overall population: patients with moderate and severe acne vulgaris at Week 12 (combined IGA=3 and 4, MI, ITT population)

Efficacy parameters	**Adapalene+BPO 0.3%/2.5% gel N=217**	**Adapalene+BPO 0.1%/2.5% gel** N=217[a]	**Vehicle gel N=69**
Success Rate (minimum 2-grade improvement and IGA "clear" or "almost clear")	33.7%[b]	27.3%	11.0%
Change in Inflammatory Lesions, Mean absolute (percent) reduction	27.8[b] (68.7%)	26.5 (69.3%)	13.2 (39.2%)
Change in Non-inflammatory Lesions, Mean absolute (percent) reduction	40.5[b] (68.3%)	40.0 (68.0%)	19.7 (37.4%)

MI= Multiple Imputation; ITT= Intent-to-treat

a) This study was not designed or powered to compare formally the efficacy of adapalene/benzoyl peroxide 0.3%/2.5% to the lower strength adapalene 0.1% / benzoyl peroxide 2.5% , nor to compare the lower strength adapalene 0.1% / benzoyl peroxide 2.5% to the Vehicle gel

b) $p<0.001$ vs Vehicle

Results of primary efficacy analyses in the severe acne population are shown in Table 3.

Table 3: Clinical efficacy in patients with severe acne vulgaris (IGA =4, MI, ITT population)

Efficacy parameters	**Adapalene+BPO 0.3%/2.5% gel N=106**	**Adapalene+BPO 0.1%/2.5% gel** N=112	**Vehicle gel N=34**
Success Rate (minimum 2-grade improvement and IGA "clear" or "almost clear")	31.9%[a]	20.5%	11.8%
Change in Inflammatory Lesions, Mean absolute (percent) reduction	37.3[b] (74.4%)	30.2 (68%)	14.3 (33.0%)
Change in Non-inflammatory Lesions, Mean absolute (percent) reduction	46.3[b] (72.1%)	43.9 (68.4%)	17.8 (30.8%)

MI= Multiple Imputation; ITT= Intent-to-treat
[a] p=0.029 vs Vehicle
[b] p<0.001 vs Vehicle

Adapalene/benzoyl peroxide 1 mg/g + 25 mg/g gel was included in this trial as a reference therapy. In subjects graded as "moderate" (IGA Grade 3), adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel showed no efficacy advantage compared with the reference therapy. In the analysis in subjects graded as "severe" (IGA Grade 4), adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel achieved a greater efficacy over vehicle with a treatment difference of 20.1% (31.9% vs 11.8%; 95% CI: [6.0%,34.2%)], p=0.029), whereas the reference therapy did not (treatment difference vs vehicle of 8.8%).

The effect of adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel on acne scarring was investigated in the OSCAR study. This was a multi-centre, randomized, investigator-blinded, vehicle-controlled trial using intra-individual comparison (right half-face vs. left half-face) investigating male and female subjects aged 16 to 35 years (n=67) with moderate to severe facial acne vulgaris, with an average mean number of acne lesions of 40 acne lesions (18 inflammatory lesions, 22 non-inflammatory lesions) on each side. The vast majority of subjects had a global moderate severity of acne (93%). Both sides were well-balanced regarding the acne lesions, the severity of acne scars was 12 scars on each side with a majority of 2-4 mm scars. Majority of subjects had a globally mild (63%) severity of scars and about 30% had moderate severity.

Male or female subjects aged 16 to 35 years inclusive and with skin phototype of I to IV on Fitzpatrick's scale were included in this study.

The enrolled population were mainly females (65.7%), and most subjects were categorized as mostly white by race (86.6%) and rest Asians (13.4%), ethnicity was not captured. The most frequent skin phototypes were II (47.8%) and III (34.3%) and rest IV (13.4%) and I (4.5%).

All eligible subjects were randomized to receive adapalene/benzoyl peroxide 3 mg/g + 25 mg/g on one half of the face and vehicle gel on the other, once daily at night, for 24 weeks. The primary efficacy endpoint was atrophic acne scar count per half-face at Week 24.

The primary endpoint analysis showed that drug therapy reduced the total number of acne scars (see Table 4).

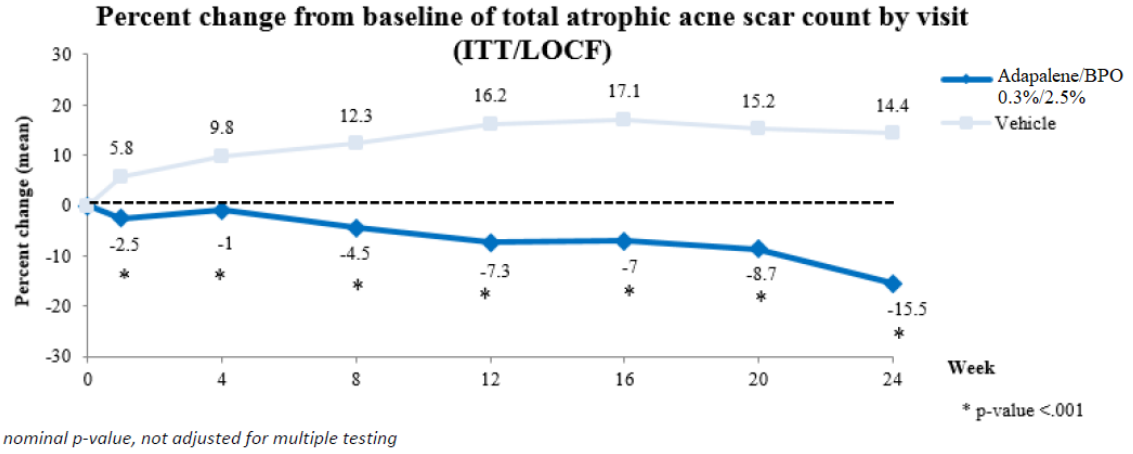
Table 4: Total acne scars (ITT/LOCF)

Total acne scars (ITT/LOCF)	**Adapalene+BPO 0.3%/2.5% gel**	**Vehicle gel**	**Treatment difference**	**Statistical result**
Mean ± SD	9.5 ± 5.5	13.3 ± 7.4	-3.7 ± 4.4	p<0.0001
Median	8.0	13.0	-3.0	
(Q1,Q3)	(6.0, 12.0)	(8.0, 19.0)	(-7.0, 0.0)	
(Min,Max)	(0, 27)	(0, 36)	(-16, 3)	

Adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel primarily reduced scars of 2-4 mm size (mean adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel9.0 ± 5.4; mean Vehicle gel 12.1 ± 7.0; mean treatment difference vs. vehicle -3.1 ± 4.1), while the reduction in scars of >4 mm was smaller (mean adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel 0.6 ± 0.8; mean Vehicle gel 1.2 ± 1.9; mean treatment difference vs. vehicle -0.6 ± 1.5).

Figure 1 shows the percent change of total atrophic scars by visit for the gel and vehicle face halves, respectively.

Figure 1



** nominal p-value, not adjusted for multiple testing*

5.2 Pharmacokinetic properties

Absorption

A pharmacokinetic study was conducted with adapalene/benzoyl peroxide 3 mg/g + 25 mg/g gel in 26 adult and adolescent subjects (12 to 33 years of age) with severe acne vulgaris. The subjects were treated with once-daily applications on all potentially affected areas during a 4 week period with, on average, 2.3 grams/day (range: 1.6-3.1 grams/day) of adapalene/benzoyl peroxide 0.3%/2.5% gel applied as a thin layer to the face, shoulders, upper chest and upper back. After 4 weeks of treatment, 16 subjects (62%) had quantifiable adapalene plasma concentrations above the limit of quantification (LOQ of 0.1 ng/mL), with a mean C_{max} of 0.16 ± 0.08 ng/mL and a mean AUC_{0-24h} of 2.49 ± 1.21 ng.h/mL. The most exposed subject had adapalene C_{max} and AUC_{0-24h} values of 0.35 ng/mL and 6.41 ng.h/mL, respectively.

Pharmacokinetics studies conducted with both adapalene/benzoyl peroxide gels (1 mg/g + 25 mg/g and 3 mg/g + 25 mg/ghave evidenced that the transdermal absorption of adapalene is not affected by benzoyl peroxide.

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.

Environmental Risk Assessment (ERA):
Environmental risk assessment studies have shown that adapalene has the potential to be very persistent, and toxic to the environment (see section 6.6).

Environmental risk assessment studies have shown that adapalene may pose a risk for aquatic compartment.

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): 3 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 15 g
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

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8. MARKETING AUTHORISATION NUMBER(S)

RVG 133315

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

Laatste gedeeltelijke wijziging betreft rubriek 6.3: 9 maart 2026