SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
AKNEFLOKS 1% cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 g cream contains

Active substance(s):

Nadifloxacin	10 mg

Excipient(s):

Methyl paraben (E218)	1.50 mg
Cetyl alcohol	50 mg
Stearyl alcohol	50 mg
Cetostearyl alcohol	10 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Cream
Almost white cream

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
AKNEFLOKS is indicated for the topical treatment of acne vulgaris and superficial skin infections.

4.2. Posology and method of administration
AKNEFLOKS should applied topically twice per day in the morning and at bedtime by spreading a thin layer of the cream to the affected area. Prior to applying the medication, the affected area should be washed and dried thoroughly. Contact with the eyes and lips should be avoided (see 4.4 Special warnings and precautions for use). AKNEFLOKS should be applied using a cotton/cloth to prevent contaminations.
AKNEFLOKS should not be used with pore-clogging ingredients.

Frequency of administration and duration of the treatment:
Treatment duration is generally up to 8 weeks.

Method of administration:
It is applied externally.

Additional information for special populations:
Renal/hepatic failure:
It is not applicable because of the route of administration.

Pediatric population:
The safety and efficacy of AKNEFLOKS has not been established in newborns and children. Therefore, AKNEFLOKS should not be used in children below 14 years of age

Geriatric population:
No special usage.

4.3. Contraindications
AKNEFLOKS is contraindicated in patients who are allergic to nadifloxacin or any of the other ingredients in the formulation.

4.4. Special warnings and precautions for use
The safety and efficacy of AKNEFLOKS has not been evaluated adequately in children below 14 years of age. Therefore, it is not recommended for use in patients in this age group.

Contact with the eyes and other mucous membranes should be avoided. In case of accidental contact, eyes or mucous membranes should be washed with plenty of warm water. Hands should be washed after applying the cream to prevent accidental applying to other areas. The product should not be applied to wounds such as cuts.

In patients treated with other systemic quinolones, it is known that photosensitivity reactions are occur. Although animal and human studies showed that nadifloxacin has not phototoxic and photoallergic effects, cream base can increase photosensitivity reactions. However, there is no experience for long-term exposure to sunlight or artificial UV irradiation when using AKNEFLOKS. Therefore, patients treated with AKNEFLOKS should avoid exposure to artificial UV irradiation (UV lamps, sunbathing, solarium) and if possible, to sunlight.

If hypersensitivity reactions such as erythema, itching and papules or severe irritation occur, AKNEFLOKS should be discontinued.

As AKNEFLOKS contains cetyl alcohol, stearyl alcohol and cetostearyl alcohol, it can cause local skin reactions (e.g. contact dermatitis)..

This medicinal product contains methyl paraben (E218) which may cause allergic reactions which can possibly be delayed.

4.5. Interaction with other medicinal products and other forms of interaction
AKNEFLOKS is very slowly absorbed through human skin following the administration (see 5.2 Pharmacokinetic properties) and therefore, interaction with other systemic drugs administered concurrently is very unlikely. There is no evidence that the efficacy of systemic drugs is influenced by the topical use of AKNEFLOKS.

AKNEFLOKS has a potential for skin irritation, and therefore it is possible that concomitant use of peeling agents, astringents and aromatic agents or irritant agents such as alcohol may produce additive irritant effects.

Two studies in healthy controls and patients with grade I-II acne vulgaris have demonstrated that concomitant use of AKNEFLOKS with other anti-acne agents does not increase the potential cumulative irritation and does not change the safety profile of product.

Additional information for special populations:
No interaction studies have been conducted on special populations.

ediatric population:
No interaction studies have been performed in the pediatric population.

4.6. Fertility, pregnancy and lactation
General advise:
Pregnancy category B

Women of childbearing potential/Birth control (Contraception):
There is no adequate data regarding the effects of nadifloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects on pregnancy /and-or/ embryonal/foetal development/ and-or/ parturition/ and-or/ postnatal development. The potential risk for humans is unknown (see Section 5.3).

Pregnancy
Caution should be exercised when prescribing to pregnant women.

Breast-feeding
Nadifloxacin passes into breast milk in quantities which can affect the suckling child when administered in therapeutic doses of AKNEFLOKS to the breastfeeding women. AKNEFLOKS should not be used during lactation. AKNEFLOKS should not be applied to the breast area during lactation.

Fertility:
There is no clinical data regarding the effects of nadifloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects on pregnancy /and-or/ embryonal/foetal development/ and-or/ parturition/ and-or/ postnatal development. The potential risk for humans is unknown (see Section 5.3).

4.7. Effects on ability to drive and use machines
Neither the pharmacodynamic profile, nor the clinical experience suggest that nadifloxacin could have any effect on the ability to drive and use machines

4.8. Undesirable effects
The undesirable effects were classified according to the following frequencies:
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)
Unknown (cannot be estimated based on available data).

Vascular disorders
Uncommon: Flushing

Skin and subcutaneous tissue disorders
Common: Itching
Uncommon: Pustule, dryness, contact dermatitis, irritation, burning sensation

Post-marketing data:
Isolated reports: Erythema, urticaria, hypopigmentation of the skin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 Turkish Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel.: 0 800 314 00 08; fax: 0 312 218 35 99).

4.9. Overdose and treatment

AKNEFLOKS is not to be taken orally and is for topical use only. If the medication is applied excessively and repeatedly, no more rapid or better results will be obtained and marked redness and discomfort may occur.

Nadifloxacin revealed a very low acute toxicity with the minimum lethal dose greater than 5000 mg/kg in rats and mice when taken orally.

Unless the amount accidentally ingested is small, an appropriate method of gastric emptying should be considered

5. PHARMACOLOGIC PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives for treatment of acne.

ATC Code: D10AF

Nadifloxacin is a synthetic bactericidal quinolone with a broad spectrum antibacterial activity against aerobic Gram-positive and Gram-negative and anaerobic bacteria, including *Propionibacterium acnes* and *Staphylo*coccus *epidermidis*.

Nadifloxacin showed potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), which was similar to potency against methicillin-sensitive *Staphylococcus aureus* (MSSA). The drug was also active against quinolone-resistant new MRSA. Nadifloxacin does not show cross-resistance with other new quinolones. Since this antimicrobial agent has been developed for topical use only, a standardized breakpoint for sensitivity to nadifloxacin has not been established in EUCAST or CLSI guidelines. The breakpoint was given to be >8 mg/L or >12 mg/L in many publications and resistance rate is negligible for all studied microorganisms. Also, the breakpoint for sensitivity to nadifloxacin was established to be ≥4 mg/L in an "in vitro" study isolated from acne patients in Germany. For the breakpoint, resistance rate against P. acnes, MSSA, MRSA and *Staphylococcus epidermidis* is very low compared to erythromycin, ciprofloxacin and clindamycin. The bactericidal action of Nadifloxacin results from the inhibition of the DNA gyrase (topoisomerase II) and topoisomerase IV bacterial enzymes. These enzymes are essential for the replication, transcription and repair of bacterial DNA. The results obtained from analysis of patients with follicular acne selected for clinical studies showed that nadifloxacin significantly reduces the number of *Propionibacterium acnes* and other microorganisms in follicles compared to the control group treated with cream base.

5.2. Pharmacokinetic properties

General characteristics

Absorption

After Nadifloxacin is applied to the skin with acne, the absorption amount of nadifloxacin is not exactly known but it is known to incomplete. The degree of absorption is dependent on the state of the stratum corneum. It was showed that percutaneous absorption of nadifloxacin in acne patients is more than those in patients with healthy skin.

Distribution
It shows extensive and rapid distribution following systemic absorption. However, it is not expected to pose a problem such as accumulation in the body since tissue levels rapidly decrease. The mean plasma concentration is 1 and 3 ng/ml.

Biotransformation
After the absorption, both unchanged Nadifloxacin and its metabolites were found in urine and faeces. Metabolization include oxidation and conjugation processes.

Elimination
Following a single topical application of 10 g Nadifloxacin to normal human back skin, the mean peak plasma level was determined to be 0.54 ng/mL and the plasma concentration decreases with half-life of mean 12.7 hours. The plasma concentration reached a steady state on Day 5 of repeated administration study when nadifloxacin 1% cream was applied at 5 g twice daily to normal healthy individuals for a period of 7 days. The plasma concentration reached a peak of 1.34 ng/ml at 8 hours post-final dosing. Mean urinary recovery was 0.013% of the administered nadifloxacin dose during a period of 192 hours.

5.3. Preclinical safety data
Preclinical data based on conventional studies of safety in humans revealed no special hazard for pharmacology, repeated dose toxicity, carcinogenic potential and photocarcinogenic potential and toxicity to reproduction.

Local toxicity studies showed a potential for mild skin irritation but, there was no evidence regarding to the delayed hypersensitivity reactions, phototoxicity or photoallergic reactions.

The mild irritant effect of Nadifloxacin cream for eyes was observed in rabbits. However, this irritation was reduced by washing with warm water after applying.

Although systemic quinolones are known to induce damage to the cartilage of the long bones in young animals, there was no evidence for the toxic effect of high oral dose nadifloxacin on joints, especially in young dogs, a sensitive species.

The genetic toxicity profile of nadifloxacin is similar to other quinolones profile on the market. It was showed that some quinolones increase photocarcinogenicity induced by UVA in mice exposed to the ultraviolet irradiation during treatment.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Methyl paraben (E218)
Phenyl ethyl alcohol
Triethanolamine
Glycerin
Cetyl alcohol
Stearyl alcohol
Cetostearyl alcohol
Oleic acid
Ethyl alcohol
Purified water

6.2. Incompatibilities
There are no any known incompatibilities.

6.3. Shelf life
24 months

6.4. Special precautions for storage
Store at room temperature below 25°C.

6.5. Nature and contents of container
It is marketed in aluminum tubes containing 30 grams of cream closed with HDPE cap.

6.6. Special precautions for disposal
Unused medicinal products or waste materials should be disposed of according to the "Regulation for the Disposal for Medicinal Waste" and "Regulation for the Control of Packaging and Packaging Waste".

7. MARKETING AUTHORISATION HOLDER
Berko İlaç ve Kimya Sanayi A.Ş.
Yenişehir Mah. Özgür Sok. No: 16-18 Ataşehir/İstanbul – Turkey
+90 216 456 65 70 (Pbx)
+90 216 456 65 79 (Fax)
info@berko.com.tr

8. MARKETING AUTHORISATION NUMBER(S)

255/39

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorization: 25/12/2013
Date of latest renewal: 11/02/2019

10. DATE OF REVISION OF THE TEXT

05.03.2019