NADEE®
(Nadifloxacin)

1. NAME OF THE PRODUCT
NADEE® (Nadifloxacin) 1% w/w Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
NADEE® 1% w/w Cream
Each gram contains:
Nadifloxacin MS.....10mg

3. PHARMACEUTICAL FORM
Topical Cream.

Appearance: White to off white cream.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
NADEE® is indicated for the topical treatment of acne vulgaris and superficial skin infections.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
NADEE® 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. **NADEE®** should be applied using a cotton/cloth to prevent contaminations. **NADEE®** should not be used with pore-clogging ingredients.
Method of administration:
It is applied externally.
Frequency of administration and duration of the treatment: Treatment duration is generally up to 8 weeks.
Additional information for special populations:
Renal/hepatic failure: It is not applicable because of the route of administration.
Paediatric population: The safety and efficacy of Nadifloxacin has not been established in newborns and children. Therefore, Nadifloxacin should not be used in children below 14 years of age.
Geriatric population: No special usage.

4.3. CONTRAINDICATIONS:

Nadifloxacin is contraindicated in patients who are allergic to Nadifloxacin or any of the other excipients in the formulation.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

The safety and efficacy of Nadifloxacin 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 Nadifloxacin. Therefore, patients treated with Nadifloxacin 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, Nadifloxacin should be discontinued. As Nadifloxacin contains cetyl alcohol and stearyl alcohol, it can cause local skin reactions (e.g. contact dermatitis).

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Nadifloxacin is very slowly absorbed through human skin following the administration 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 Nadifloxacin. Nadifloxacin 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 Nadifloxacin 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.

Paediatric population: No interaction studies have been performed in the paediatric population.

4.6. FERTILITY, PREGNANCY AND 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.

Pregnancy: Pregnancy category B. 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 Nadifloxacin to the breast-feeding women. Nadifloxacin should not be used during lactation. Nadifloxacin should not be applied to the breast area during lactation.

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 frequencies defined as: Very common (≥1/10); Common (≥1/100 and <1/10); Uncommon (≥1/1000 and <1/100); Rare (≥1/10,000 and <1/1000); Very rare (< 1/10,000); Not known (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.

4.9. OVERDOSE:

Nadifloxacin 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 5000mg/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. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Anti-infectives for treatment of acne.

ATC Code: D10AF.

NADEE® 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 *Staphylococcus epidermidis*.

Mechanism of action: 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 >8mg/L or >12mg/L in many publications and resistance rate is negligible for all studied microorganisms. Also, the breakpoint for sensitivity to nadifloxacin was established to be ≥4mg/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. PHARMACOKINETICS:

Absorption: After Nadifloxacin is applied to the skin with acne, the absorption amount of nadifloxacin is not exactly known but it is known too 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 3ng/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 10g Nadifloxacin to normal human back skin, the mean peak plasma level was determined to be 0.54ng/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 5g twice daily to normal healthy individuals for a period of 7 days. The plasma concentration reached a peak of 1.34ng/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:

- Liquid paraffin
- Glycerol (Glycerine)
- Stearyl alcohol
- Cetyl alcohol
- Cetomacrogol
- White petrolatum
- Sodium hydroxide
- Triethanolamine
- Disodium Edetate
- Purified water

6.2. INCOMPATIBILITIES:

There are no any known incompatibilities.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C, and protect from heat, light and freezing.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Plastic laminated tube, pack size is 10g.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused medicinal products must be disposed of in accordance with local regulations in force.

6.7. DRUG PRODUCT SPECIFICATIONS:

SAMI's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

045314

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

11th April, 2007

10. DATE OF REVISION OF THE TEXT

نیڈی کریم

(نیڈی فلاکساسن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں

بچوں کی پہنچ سے دور رکھیں

صرف بیرونی استعمال کے لئے ہے

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور منجمد ہونے سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی