SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aknemycin® Plus

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 g of solution contains:
Erythromycin 4.0 g,
Tretinoin 0.025 g.

Excipients with known effect:
This medicinal product contains 752 mg alcohol (ethanol) per ml.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for application to the skin.
Aknemycin Plus is a clear, light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

All forms of acne, both non-inflammatory forms with comedones and inflammatory forms with papules and pustules, particularly in the case of fat-rich skin.

4.2 Posology and method of administration

Posology

Unless otherwise prescribed, Aknemycin Plus is applied once or twice daily to the cleansed skin.

Method of administration

For application to the skin.

Aknemycin Plus is applied directly from the special applicator bottle on to the skin. This enables the product to be applied simply, hygienically and sparingly. The applicator is constructed in such a way that no particles of dirt can be transferred from the skin to the solution.
The duration of application depends on the condition of the skin, but should not exceed twelve weeks. Consistent application makes a significant contribution to the success of the therapy.

4.3 Contraindications

- Pregnancy (see section 4.6)
- Women planning a pregnancy
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Acute eczemas

- Rosacea
- Acute inflammations of the skin (e.g., sunburn), particularly in the area of the mouth (perioral dermatitis).

4.4 Special warnings and precautions for use

As with other macrolides, rare serious allergic reactions, including acute generalised exanthematous pustulosis (AGEP) have been reported. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.
Aknemycin Plus must not be allowed to come into contact with the eyes. Should this nevertheless occur, thorough rinsing with water is recommended.
Aknemycin Plus should not be applied too close to the lips or nostrils.
The hands should be thoroughly washed if Aknemycin Plus comes into contact with the fingers in spite of the use of the applicator.

For use during pregnancy and the lactation period, see section 4.6.

This medicinal product contains 752 mg alcohol (ethanol) per ml. It may cause burning sensation on damaged skin.
Do not light a cigarette or expose yourself to open flames until the medicine has dried completely

4.5 Interaction with other medicinal products and other forms of interaction

Photosensitivity may occur during therapy. The skin irritation described in the section "Undesirable effects" may be exacerbated by ultraviolet radiation (natural sunlight, sunlamps, solaria) and x-rays, as well as bathing in water containing chlorine or salts. This applies in particular to individuals who are exposed to sunlight for prolonged periods due to their profession, as well as to patients who are particularly sensitive to light. During therapy with Aknemycin Plus patients should avoid exposure to direct sunlight or other ultraviolet rays including sunlamps or sun beds. Any sunburn should be allowed to heal before the start of treatment with Aknemycin Plus.
The simultaneous application of other skin preparations should be avoided, as this may exacerbate any skin irritation that is present.

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

Aknemycin Plus is contraindicated (see section 4.3) in pregnancy, or in women planning a pregnancy.

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

Lactation
In order to avoid direct contact with the infant, Aknemycin Plus must not be used in the area of the breast during the lactation period.

4.7 Effects on ability to drive and use machines

No particular precautions are required.

4.8 Undesirable effects

The following frequency categories are used for the evaluation of undesirable effects:

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	(frequency cannot be estimated from the available data)

Skin and subcutaneous tissue disorders
There may be rare cases of reduced pigmentation of the skin, as well as skin irritation in the form of reddening, burning, drying out and desquamation. In very rare cases the above symptoms may also be an expression of a hypersensitivity reaction (allergic contact eczema). At the beginning of treatment the acne may appear to worsen, with an increase in the number of inflammatory symptoms; this is a sign that the medicine is beginning to act and is mostly of a temporary nature. Treatment with Aknemycin Plus should therefore not be discontinued. However, the frequency of application can be reduced temporarily.

Not known: acute generalised exanthematous pusulosis (AGEP)

Reporting of side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" that appears on the homepage of the Ministry of Health's website (www.health.gov.il) which links to an online form for reporting side effects, or by the following link: https://sideeffects.health.gov.il/
In addition, you can report by emailing the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-acne preparations for topical use, anti-infectives, erythromycin in combination with tretinoin. ATC code: D10AF52

Erythromycin:
Erythromycin possesses a strong antibacterial effect with respect to Propionibacterium acnes, a skin germ to which a significant role in the pathogenesis of acne is attributed.
Clinical trials have shown that after topical application erythromycin penetrates into the sebaceous gland ducts, where its bacteriostatic effect unfolds. The anti-microbial activity corresponds to that of penicillin, comprising gram-positive and some gram-negative germs. Erythromycin is reversibly bound to the 50 S subunit of the ribosomes of the bacteria, thus inducing inhibition of their protein biosynthesis.

Restriction of the enzymatic activity of the bacterium inhibits lipolysis of the skin surface lipids, reducing the concentration of free fatty acids.
Erythromycin results in clinical improvement to the acne efflorescences; the local antibiotic therapy is comparable in terms of its efficacy to the systemic administration of the antibiotic. Furthermore, erythromycin also has a direct anti-inflammatory effect. The alcoholic base of Aknemycin Plus supports the antibacterial effect of erythromycin, while at the same time removing the skin sebum.

Tretinoin:
Tretinoin (vitamin A acid) is a deep-acting keratolytic agent. Tretinoin belongs to the group of retinoids and has a stimulating effect on the proliferation of the cornified cells of the skin. It binds to a cellular protein (CRABP) and in this way infiltrates the cell nucleus. The adhesiveness of the cornified cells formed under the influence of tretinoin is reduced and the development of cornified cell “plugs” in the acroinfundibulum of the follicle channel prevented. Tretinoin leads to comedolysis and a reduction in the size of the sebaceous glands. Open comedones are loosened and ejected, while closed comedones are transformed more rapidly into open ones and eliminated. During application with tretinoin the local effect is initially accompanied by irritation and an increase in the blood supply to the skin. Comedones that are not clinically visible are transformed into inflammatory ones and ejected, while persistent papules and nodes are removed more quickly.
The skin irritation caused by tretinoin is largely attenuated by the combination with erythromycin.
Aknemycin Plus is well tolerated by the skin; seborrhoeic skin conditions are normalised. In the hypersensitivity test according to Magnusson-Kligman there were no indications of hypersensitivity caused by Aknemycin Plus.

5.2 Pharmacokinetic properties

After the topical application of erythromycin the substance cannot be detected in the serum; absorption therefore only occurs in quantities that are not detectable, if at all.
Details on the absorption of tretinoin fluctuate between 0.5 % and a maximum of 24 %. The substance is rapidly degraded to polar metabolites and excreted via the intestines and kidneys; there is no storage in the liver. Systemic pharmacodynamic effects as a consequence of local treatment are not to be expected, particularly in view of the concentration used in the preparation.

5.3 Preclinical safety data

With the exception of a hypersensitivity test (see Local tolerance), no additional toxicological studies have been performed on animals with Aknemycin Plus.

Acute toxicity
Erythromycin:

Numerous animal trials have shown that erythromycin is a substance with a low level of acute toxicity.

Tretinoin:
Investigations into the acute toxicity of tretinoin in rats and mice produced LD_{50} values of approx. 2.1 g/kg when the substance was administered orally and 0.8 g/kg in the case of intraperitoneal administration. Tretinoin therefore displays low levels of acute toxicity.

Subchronic and chronic toxicity
Erythromycin:
Investigations into the chronic toxicity of the substance when administered orally to two species of animal showed no changes caused by the substance.

Tretinoin:
The toxic doses are approximately 2,000 – 20,000 times higher than the therapeutic quantities of the active substance administered to humans. See "Local tolerance".

Mutagenic and carcinogenic potential
Erythromycin:
Erythromycin has no mutagenic effect; there are no indications of carcinogenic activity.
An in vitro analysis using several test systems did not show any indications of mutagenic properties for erythromycin. Feeding trials over a period of two years on rats and mice provided no indications of carcinogenic potential. Dose-dependent granulomas occurred in the livers of male and female rats.

Tretinoin:
Tretinoin has so far only been tested on bacteria with respect to its mutagenic effects. These trials produced a negative result. Long-term investigations into any carcinogenic potential have not been carried out. The results of the photocarcinogenesis and cocarcinogenesis observed in animal experiments which are occasionally a subject of discussion cannot be transferred automatically to human skin.

Local tolerance
In the maximisation test performed on guinea pigs the combination preparation did not display any hypersensitivity of the skin.

Erythromycin:
Erythromycin is well tolerated when applied locally. The substance does not have a photosensitising effect. The sensitisation potential of erythromycin is considered to be very low.

Tretinoin:
After the topical application of tretinoin (0.05% gel) no systemic intolerance is to be expected. Reversible skin irritation may occur locally with erythema, oedema, the rejection of superficial layers and epithelium proliferation. Occasionally, dose-dependent lightening of the skin may occur as a consequence of the inflammatory reaction; however, no reduction in pigment is to be expected with the concentrations that are normally applied.

The rabbit eye showed no irritation after the local application of tretinoin; the mucous membranes reacted less sensitively than the normal cornified skin.

Reproduction toxicity
Erythromycin:
Fertility and teratogenicity studies do not provide any indication that erythromycin leads to reproductive disturbances or damage when applied locally to humans.

Tretinoin:
In rats and rabbits to which the substance was administered topically in doses of up to 1 mg/kg a day there were no teratogenic or other embryotoxic findings if oral intake of the active substance by the mothers was prevented. The plasma levels for tretinoin and effective metabolites lay within the range of endogenous concentrations and did not give any indications of appreciable percutaneous absorption.
Tretinoin administered systemically (orally, subcutaneously) caused deformities in all species investigated (rats, mice, hamsters, rabbits, monkeys). The lowest teratogenic dose for the most sensitive species (mouse) is between 1 – 3 mg a day for subcutaneous administration.
There have been individual reports of birth defects in children whose mothers had been treated topically with tretinoin during pregnancy. A cohort study involving children whose mothers were exposed to topical tretinoin treatment during the first trimester of pregnancy did not produce any accumulation of deformities in comparison to a group of women who had not been exposed. No controlled prospective studies have been performed on pregnant women. The tretinoin blood levels that produce teratogenic effects are not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 100 %; glycerol 85 %; copovidone.

6.2 Incompatibilities

Light, oxidising agents.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening the bottle: 6 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Solution for application to the skin:
1 applicator bottle of 25 ml
1 applicator bottle of 50 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Aknemycin is an alcohol-based product and is flammable.

7. MANUFACTURER

Almirall Hermal GmbH, Scholtzstrabe 3, D-21465 Reinbek Hamburg, Germany

8. REGISTRATION HOLDER

Neopharm Ltd., Hashiloach 8, P.O. Box 7063, Petach Tiqva 49170, Israel

9. REGISTRATION NUMBER

135-52-30266

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