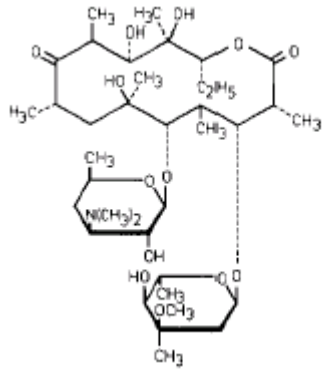
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aknemycin®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 g of solution contains 0.2 g of erythromycin.



Structural formula of erythromycin

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cutaneous solution

Aknemycin is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

All forms of acne, in particular inflammatory forms with papules and pustules.

4.2 Posology and method of administration

Posology
Generally the solution should be applied twice a day.

Method of Administration
The bottle has a special applicator; with this Aknemycin can be applied directly on to the skin.

The applicator bottle is prepared for use each time by pressing vigorously on the applicator beforehand with the reversed cap. This releases the safety mechanism and Aknemycin can be applied.

Treatment with Aknemycin should not be longer than 4 – 6 weeks.

4.3 Contraindications

Aknemycin must not be used in cases of
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 should not be allowed to get into the eyes.

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

None known to date.

4.6 Fertility, Pregnancy and lactation

Pregnancy
Aknemycin can be used during pregnancy as the active substance erythromycin is not absorbed percutaneously to any significant extent and therefore no undesirable effects on the unborn child are to be expected.

Lactation
Aknemycin can be used during the lactation period. In order to avoid the oral intake of erythromycin by the infant during the first few weeks of life, the child's mouth should be prevented from coming into contact with the areas of the body that have been treated.

4.7 Effects on ability to drive and use machines

Not relevant.

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
Very rare: drying, reddening, burning and itching of the skin. In these cases it is appropriate to continue treatment with the Aknemycin preparations Aknemycin Ointment or Aknemycin Emulsion, as these dry out the skin to a lesser extent. Aknemycin Solution can also be applied alternately with these preparations.

In individual cases the above symptoms may also be signs of a hypersensitivity reaction to the active substance or any of the excipients (allergic contact eczema).

Not known: acute generalised exanthematous pustulosis (AGEP)

After prolonged treatment the symptoms may become worse through the development of resistance and gram-negative folliculitis.

Reporting 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
and emailed to 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 for treatment of acne – Erythromycin

ATC code: D10AF02

The erythromycin contained in Aknemycin has a bacteriostatic effect on all germs that play a role in the development of acne, in particular *Propionibacterium acnes* (Corynebacterium acnes), *Staphylococcus aureus* and *Staphylococcus epidermidis*. This also includes inhibition of lipolysis of the sebum lipids.

Furthermore, erythromycin possesses a direct anti-inflammatory effect.

Spectrum of Activity of Erythromycin
The following spectrum of activity of erythromycin only includes *in vitro* data. This is therefore not necessarily associated with an assertion of the clinical efficacy of the active substance with respect to the pathogens, which are assessed as sensitive, intermediary or resistant.

Sensitivity
For the erythromycin base the following provisional minimum inhibitory concentrations (MIC) are proposed:
for sensitive germs ≤ 1 mg/l, for germs of medium sensitivity (intermediary) 2 – 4 mg/l and for resistant germs ≥ 8 mg/l [limiting values (breakpoints) according to DIN 58 940]. Based on this procedure, too high resistance ratios result for topical application in cases of doubt because higher concentrations are achievable locally.

Table: In vitro Therapeutic Spectrum of Erythromycin [Expert Report dated 2003].

	In vitro Data
Relevant pathogens with respect to the claimed indication	Lowest and highest ascertained value (range) for the acquired resistance in Germany (%)
Sensitive aerobic gram-positive	
Staphylococcus aureus*	86.0 – 87.9
Staphylococcus epidermidis	31.0 – 40.9
Sensitive anaerobic gram-positive	
Propionibacterium acnes	88.6
Intermediary aerobic gram-positive	
Staphylococcus aureus*	2.6 – 6.0
Staphylococcus epidermidis	0.9 – 9.4
Intermediary anaerobic gram-positive	
Propionibacterium acnes	
Resistant aerobic gram-positive	
Staphylococcus aureus*	7.8 – 11.1
Staphylococcus epidermidis	58.2 – 62.4
Resistant anaerobic gram-positive	
Propionibacterium acnes	11.4

* Methicillin-sensitive

The resistance ratios contained in the table with respect to systemically applicable erythromycin cannot simply be transferred to topical treatment. The sensitivity or resistance of a pathogen depends on the achievable concentration at the site of the desired effect. In individual cases of topical antibiotic application it is not known today how high the active substance concentration at the various locations of the desired effect really is. In the case of topical acne treatment it can be assumed that pathogens which have been classified as "non-resistant" according to the interpretation criteria for systemic therapy are recorded without difficulty. The question remains unanswered as to whether "resistant" bacteria can also be reached by the relatively high local concentrations. It is known that the populations of *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Propionibacterium acnes* can display different levels of resistance on and in the skin of the same acne patient. The important factor for therapeutic success is not the entire elimination of all (including the "resistant") germs, but a clear reduction in the germ count.

The good clinical efficacy of Aknemycin in various forms of acne has been demonstrated in placebo-controlled, double-blind and open studies. Local antibiotic treatment with Aknemycin is comparable in terms of its efficacy with the systemic administration of antibiotics.

So far there have been no reports of photosensitisation resulting from the topical application of erythromycin.

The alcoholic base of the Aknemycin solution supports the antibacterial effect of the erythromycin and also dissolves the sebaceous matter.

5.2 Pharmacokinetic properties

After the topical application of Aknemycin the active substance erythromycin is not absorbed percutaneously to any significant extent. Even after several weeks of the application of Aknemycin over a large area it was not possible to detect any erythromycin in the serum of the patients.

5.3 Preclinical safety data

The acute and chronic oral toxicity of erythromycin is low.

Preclinical investigations into mutagenicity and a long-term investigation to determine its tumour-producing potential were negative.

Reproduction studies on several animal species with erythromycin and its various salts have not produced any indications of fertility disorders or embryo toxicity/foetotoxicity.

Bioavailability
Erythromycin is released from Aknemycin and penetrates into the sebaceous gland ducts, where it has a bacteriostatic effect. This has been confirmed by *in vivo* and *in vitro* studies.

With the help of a special method for selectively determining the follicular flora (cyanoacrylate method) it has been shown in vivo that Aknemycin induces a significant reduction in Propionibacteria acnes, Micrococcaceae and the total germs count.

In vitro auxanogram tests (perforated plate tests) have been performed on Propionibacteria acnes and staphylococci, amongst others. The inhibition zones found for the Aknemycin were considerably larger in comparison to the alcohol-containing base.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous 9.25 g
Lauryl polyglycol phosphate
Glycerol
Povidone

6.2 Incompatibilities

Oxidants and water inactivate erythromycin.

6.3 Shelf life

The expiry date of the product is indicated on the package materials.

Shelf-life after first opening: 6 months

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Glass bottle with applicator and plastic screw cap

Pack size: 25 ml

6.6 Special precautions for disposal and other handling

No special requirements.

Aknemycin is an alcohol-based product and is flammable.

7. MANUFACTURER

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

8. REGISTRATION HOLDER

Neopharm Ltd.
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Petach-Tiqva 4917001
Israel

9. REGISTRATION NUMBER

064-70-22653

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