

(19) AUSTRALIAN PATENT OFFICE

(54) Title

Use of amide derivative of GE 2270 factor A3 for the treatment of acne

(51)⁶ International Patent Classification(s)

C07D 513/22 8/06
 (2006.01) 20060101ALI2006031
A61K 8/00 (2006.01) OBMJP **A61K**
A61K 8/02 (2006.01) 8/49
A61K 8/06 (2006.01) 20060101ALI2006031
A61K 8/49 (2006.01) OBMJP **A61K**
A61K 31/4545 31/4545
 (2006.01) 20060101ALI2006031
A61K 38/12 (2006.01) OBMJP **A61K**
A61K 45/00 (2006.01) 38/12
A61P 17/10 (2006.01) 20060101ALI2005100
A61Q 19/00 (2006.01) 8BMEP **A61K**
 C07D 513/22 45/00
 20060101AFI2006031 20060101ALI2006031
 OBMJP **A61K** OBMJP **A61P**
 8/00 17/10
 20060101ALI2006031 20060101ALI2006052
 OBMJP **A61K** 1BMW0 **A61Q**
 8/02 19/00
 20060101ALI2006031 20060101ALI2006031
 OBMJP OBMJP
 OBMJP **A61K** PCT/EP03/05989

(21) Application No: 2003242647

(22) Application Date: 2003 .06 .06

(87) WIPO No: W003/105881

(30) Priority Data

(31) Number	(32) Date	(33) Country
02013268.4	2002 .06 .17	EP

(43) Publication Date : 2003 .12 .31

(43) Publication Journal Date : 2004 .02 .26

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(56) Related Art

US 6143739
 Panzer et al. Cutis, Excerpta Medica 1977, 19(1), 109-111
 US 6008225
 EP 494078

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 03/105881 A1

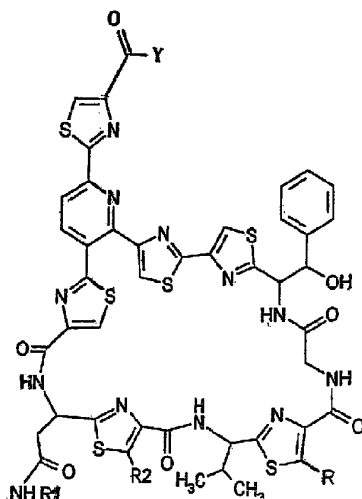
- (51) International Patent Classification⁷: **A61K 38/12**,
A61P 17/10
- (21) International Application Number: PCT/EP03/05989
- (22) International Filing Date: 6 June 2003 (06.06.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 02013268.4 17 June 2002 (17.06.2002) EP
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW).

[Continued on next page]

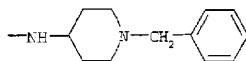
(54) Title: USE OF AMIDE DERIVATIVE OF GIE 2270 FACTOR A3 FOR THE TREATMENT OF ACNE

WO 03/105881 A1



(I)

(57) Abstract: Use of the compound of formula (I) and the pharmaceutically acceptable addition salts thereof for the manufacture of a medicament for topical treatment or prevention of acne formula (I) wherein: R represents methoxymethyl, R1 represents methyl, R2 represents methyl, Y represents the group formula (II) The compound of formula (I) and the pharmaceutically acid addition salts thereof show selective activity against propionibacterium acne and are suitable for use in a method of treatment or prevention of acne.



(II)



Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

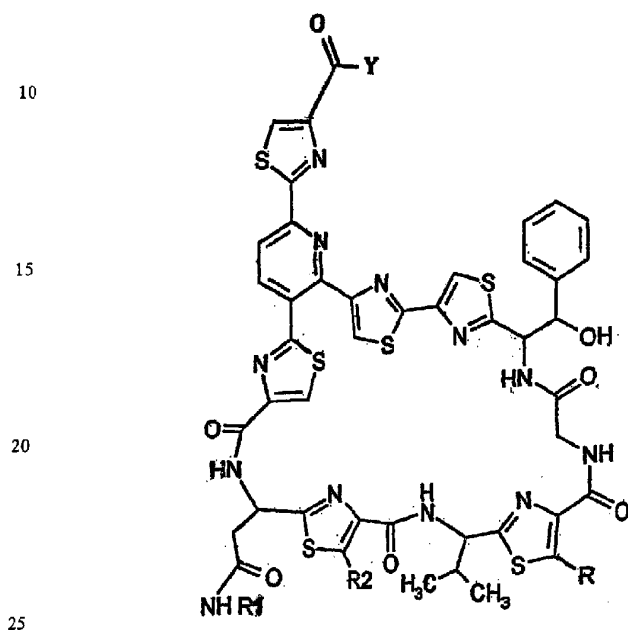
— with international search report

— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

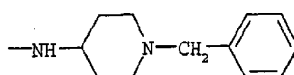
For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

USE OF AMIDE DERIVATIVE OF GE 2270 FACTOR A3 FOR THE TREATMENT OF ACNE

5 More particularly, the scope of this invention relates to the use of the compound of formula (I)



Y represents the group



and the pharmaceutically acceptable acid addition salts thereof;

for the manufacture of a medicament for the topical treatment or prevention of acne.

5 A further object of the invention is a method for topical treatment of acne in a mammal suffering of said skin disorder which comprises topically administering the compound of formula (I) above and the pharmaceutically acceptable acid addition salts thereof to said mammal in an
10 amount sufficient to provide inhibitory activity on proliferation of Propionibacterium acnes.

With the term "pharmaceutically acceptable acid addition salts", as used in this description and claims, are intended those salts with acids which from biological,
15 manufacturing and formulation standpoint are compatible with the pharmaceutical practice.

Representative and suitable acid addition salts of the compounds of formula (I) include those salts formed by standard reaction with both organic and inorganic acids
20 such as, for example, hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, trifluoroacetic, trichloroacetic, succinic, citric, ascorbic, lactic, maleic, fumaric, palmitic, cholic, pantoic, mucic, glutamic, camphoric, glutaric, glycolic, phthalic, tartaric, lauric, stearic,
25 salicylic, methanesulfonic, dodecanesulfonic acid benzenesulfonic, sorbic, picric, benzoic, cinnamic and the like.

The compound of formula (I) above is a known amide derivative of antibiotic GE 2270 factor A₃. This latter
30 compound, which corresponds to the compound of formula (I) above wherein Y represent a group hydroxy, is also a known compound. Said amide derivative of antibiotic GE 2270 factor A₃ of formula (I), its preparation by amidation of antibiotic GE 2270 factor A₃, as well as the preparation of
35 its pharmaceutically acceptable acid addition salts is

described in US 5.599.791.

Acne vulgaris, the most common chronic skin condition seen by dermatologists, is a disorder of the pilosebaceous unit characterized by papules, comedones and pustules. The face, back and chest are the areas most commonly affected as they possess a large number of sebaceous glands, about nine times the concentration found elsewhere on the body¹⁾. It affects more than seventeen million people in the US and it has been estimated that 85 percent of the adolescent population experiences this condition. Acne affects both genders with a peak incidence at 14-17 years for girls and 16-19 years for boys²⁾. It also affects 8 percent of 25-34 years-old and 3 percent of 35-44 years-old adults³⁾. However, the number of patients over the age of 25 affected by acne vulgaris is increasing. Adult women, in particular, may be affected and may experience premenstrual flares. In any case, severe acne tends to be more common in adolescent males than in people of other age-groups.

Although the primary cause of acne is end-organ hyper-responsiveness to circulating androgens triggering sebum overproduction in the follicle, an important role is also played by secondary bacterial infection that is favoured by abnormal desquamation of follicular epithelium. The increased amount of sebum produced, combined with excessive numbers of desquamated epithelial cells from the walls of the sebaceous follicle, accumulates within and distends the follicle, resulting in the formation of a clinically unapparent precursor lesion of acne vulgaris called the microcomedone. There are several explanations for ductal hypercornification. These include the comedogenic effects of certain sebaceous lipids, an androgen-controlled defect, retinoid control, local cytokine modulation and the effects of ductal bacteria⁴⁾. Propionibacterium acnes is a member of the resident bacterial flora and resides in sebaceous follicles. The anaerobic environment of the follicles that

are plugged, indeed, particularly facilitate proliferation of P. acnes causing the release of chemotactic factors and proinflammatory mediators into the follicle and surrounding dermis leading to the inflammation^{5),6),7)}. Detailed
5 investigation of cell types and adhesion molecules would support the view that the inflammation of acne is a normal type 4 response in the first 76 h^{8),9),10)}.

The clinical manifestations of these pathophysiological events include non-inflammatory closed (blackhead) or open
10 (whitehead) comedos, as well as inflammatory lesions, including papules, pustules, cysts and nodules¹¹⁾.

Acne can be divided into mild, moderate and severe based on the number of lesions and the surface of skin involved. Mild acne is characterized by open and closed
15 comedones sometimes accompanied by few superficial inflammatory lesions, moderate acne is characterized by increasing largely superficial inflammatory lesions with pustules that have the tendency to scar with time. Nodules and cysts with marked scarring characterize severe acne.

20 While acne is not a life threatening disease, it has been related to psychiatric morbidity for many years. Emotional stress can exacerbate acne, and patients with acne develop psychiatric problems as a consequence of their condition¹²⁾. Psychiatric issues associated with acne include
25 problems with self-esteem/self-confidence, body image, embarrassment/social withdrawal, depression, anxiety, anger, preoccupation with acne, frustration/confusion, limitations in lifestyle, and problems in family relationships^{13),14)}. Permanent scarring is another relevant
30 consequence of acne.

The treatment and prevention of acne includes various topical and systemic therapies and is guided by the type of clinical lesions present. Successful management of acne
requires also careful patient evaluation followed by
35 consideration of several factors related to the patient,

e.g. age, skin type, coexisting conditions, lifestyle, menstrual regularity. The ideal agent would target each of the pathogenic factors without producing adverse effects. However, no single topical therapeutic agent has yet
5 emerged that is capable of ameliorating all of the factors involved in the etiopathogenesis of acne vulgaris. Topical therapy is often preferred because of its safety compared with others forms of treatments¹⁵⁾. Current topical therapies include comedolytic agents such as tretinoin,
10 adapalene, azelaic acid, tazarotene and salicylic acid; antimicrobial agents such as benzoyl peroxide; antibiotics such as clindamycin, erythromycin and tetracycline; and anti-inflammatory agents such as sodium sulfacetamide. Oral antibiotics are often added to the treatment regimen when
15 acne does not respond satisfactorily to topical therapy. Other systemic treatments for more severe, recalcitrant acne include estrogens, antiandrogens, and isotretinoin.

The eradication of P. acnes constitutes a logical approach to effective treatment, since the mere presence of
20 this organism partially defines the disorder⁴⁾. Benzoyl peroxide exerts its bactericidal activity on P. acnes by generating reactive oxygen species in the sebaceous follicle¹⁶⁾. It is very effective in combination with either topical antibiotics or tretinoin¹⁷⁾. The major adverse effect
25 of benzoyl peroxide is local irritation, particularly pronounced at therapy initiation. Other recorded adverse effects include erythema, dryness and allergic contact dermatitis (1-3% of patients). Clothes bleaching may
30 present a problem in case of application to the chest or to the back.

Topical erythromycin and clindamycin have similar efficacy in patients with acne and are useful in the treatment of mild to moderate acne¹⁸⁾. These agents are available in a variety of formulations and are applied once
35 or twice daily. They are often used in combination with

benzoyl peroxide or tretinoin. Topical antibiotics are associated with some minor skin irritation, maybe influenced by the vehicle used. Diarrhea and pseudomembranous colitis have been associated with the use of topical clindamycin^{19), 20)}.

One of the biggest concerns with the use of antibiotics in acne therapy is the emergence of resistant strains of P. acnes and of other Gram-positive bacteria of the resident flora. P. acnes resistance is now accepted as clinical issue of increasing importance⁵⁾. Combined resistance to erythromycin and clindamycin was first reported in 1979 in the USA in 20% of follicular P. acnes isolates from acne patients treated with topical formulations of either drug²¹⁾, while resistance of P. acnes to tetracyclines was first documented in 1983 in USA in patients who were not responding well to oral antibiotic treatment²²⁾. At present, it has been estimated that 1 in 4 acne patients harbour P. acnes strains resistant to clindamycin, erythromycin, and/or tetracycline²³⁾. In 1997, 65% of 567 acne patients in UK carried resistant P. acnes strains²⁴⁾. In a recent study, antibiotic-resistant P. acnes strains were found in 28% of acne patients previously treated with antibiotics compared with only 6% of acne patients not receiving antibiotic treatment²⁵⁾. It has also been demonstrated that P. acnes strains resistant to erythromycin, clindamycin, tetracycline and a variety of related antibiotics are to be found in Europe, USA, Australia and Japan²⁶⁾. The presence of erythromycin-resistant propionibacteria on the skin surface has been shown to correlate very strongly with inadequate response during therapy with oral erythromycin²⁷⁾. Besides, it is well documented that resistant strains of coagulase-negative staphylococci within the resident skin flora increase in both prevalence and population density as duration of topical antibiotic therapy of acne increases. Acne patients represent a

considerable reservoir of resistant strains of these important nosocomial pathogens which can be transferred to close contacts²⁴⁾.

Another drawback of currently used broad spectrum antibiotics is their poor selectivity of action against P. acnes, as they are active against all other Gram-positive bacteria which normally colonize the skin. This results in the eradication of these organisms whose presence on the skin is an obstacle to and generally prevents colonization by other problematic organisms: potentially, the elimination of resident Gram-positive bacteria may favour side infections caused by difficult-to-treat Gram-negative bacteria and pathogenic fungi.

It follows a need for a new antibiotic, possibly provided with novel mechanism of action, active against strains of P. acnes both susceptible and resistant to currently used antibacterial agents; further improvement on current therapy could be achieved with an antibiotic highly selective for P. acnes because of the lower possibility of skin side infections; low frequency of selection of resistant mutants and bactericidal activity would be additional advantages which could further recommend the use of such antibacterial agent.

The selectivity of action against P. acnes should allow maintaining almost unchanged the normal Gram-positive bacterial flora of the follicles, mainly staphylococci, thus preventing possible site colonization by other disease-causing bacteria, including Gram-negative pathogens, and fungi.

Selectivity of action against P. acnes is defined as a condition where the anti-acne candidate compound to be used in the treatment or prevention of acne, at the dosage which is usually employed in the topical formulations to provoke inhibition of proliferation of P. acnes on the skin, is inactive against all other Gram-positive bacteria, which

normally colonize the skin surface thus contributing to the maintenance of its physiological conditions. In particular, bacterial strains which should not be affected by topical administration of the anti-acne candidate compound are

5 Staphylococcus aureus, Staphylococcus epidermidis, and Streptococcus pyogenes strains. A pre-requisite to achieve a reasonable certainty that the above condition of selectivity of action is met, is that the anti-acne candidate compound shows in a series of *in vitro* tests MIC

10 (Minimum Inhibitory Concentration) values against the above mentioned strains which are much higher than those displayed against Propionibacterium acnes strains which are both sensible and resistant to other antibiotics which are currently employed in the treatment of skin disorders such

15 as erythromycin and clindamycin.

This property in a therapeutic setting, i.e. topical treatment of acne, will allow application of amounts of the drug which will not substantially affect the normal Gram-positive bacterial flora of the skin, mainly staphylococci,

20 thus preventing possible site colonization by other disease-causing bacteria, including Gram-negative pathogens, and fungi.

According to this invention it has been found that the profile of activity of this amide derivative of formula (I)

25 demonstrates that the said compound selectively inhibits the growth of P. acnes at concentration that are more than 1000 times lower than those required to inhibit the growth of the above mentioned bacteria that are present on the surface of the normal skin, thus indicating that it is

30 useful for selective antimicrobial therapy of mild/moderate acne via topical administration as mono-therapy or in association with agents that possess comedolytic and anticomedogenic activity. In fact, the compound of formula (I) has selective *in vitro* activity against

35 Propionibacterium acnes, with MIC values ranging from 0.06

(80% of tested strains) to 0.25 mg/mL including isolates resistant to broader spectrum antibiotics, i.e. erythromycin, tetracyclin and clindamycin, which have been used extensively for the treatment of acne for over 30 years. Other Gram-positive species are not susceptible to the compound of formula (I), the only exception being enterococci, which are inhibited at concentrations ranging from 0.5 to 16 mg/mL. However, these strains have no relevance in the context of this invention since they are not part of the normal skin flora. The compound of formula (I) is inactive against Gram-negative bacteria and fungi.

The surprisingly high degree of selectivity action of the compound of formula (I) of this invention has been evidenced through in vitro tests wherein the minimum inhibitory concentration (MIC) against Propionibacterium acnes strains both sensitive and resistant to erythromycin and clindamicyn and against a series Staphylococcus strains have been determined. The tests have been carried out in comparison with antibiotic GE 2270 and four representative compounds (B, C, D and E) described in US 5.599.791.

The results are reported in TABLE 1 below

TABLE 1

Microorganism	strain	medium	MIC ($\mu\text{g/ml}$)				
			A	B	C	D	GE 2270
<i>Staphylococcus aureus</i>	Smith ATCC 19636	Mueller Hinton (MH)	>128	2	2	1	0.06
<i>Staphylococcus aureus</i>	Smith ATCC 19636	MH+30% bovine serum	>128	8	8	4	0.25
<i>Staphylococcus aureus</i>	MRSA	MH	>128	4	2	0.250	<0.125
<i>Staphylococcus epidermidis</i>	ATCC 12228	MH	>128	8	4	0.5	<0.125
<i>Streptococcus pyogenes</i>	C 203	MH	>128	>128	>128	8	0.25
<i>Propionibacterium acne</i>	ATCC 6919	Wilkins Chalgren (WC)	<0.125	<0.125	<0.125	<0.125	<0.125
<i>Propionibacterium acne</i>	ATCC 6922	WC	<0.125	<0.125	<0.125	0.125	<0.125
<i>Propionibacterium acne</i>	ATCC 25746	WC	<0.125	<0.125	<0.125	<0.125	<0.125
<i>Propionibacterium acne</i>	clinical isolate	WC	<0.125	<0.125	<0.125	<0.125	<0.125
<i>Propionibacterium acne</i>	clinical isolate	WC	<0.125	<0.125	<0.125	<0.125	<0.125
<i>Propionibacterium acne</i>	clinical isolate	WC	<0.125	<0.125	<0.125	0.125	0.125
<i>Propionibacterium acne</i>	clinical isolate	WC	<0.125	<0.125	<0.125	<0.125	<0.125
<i>Propionibacterium acne</i>	clinical isolate	WC	<0.125	<0.125	<0.125	<0.125	<0.125
<i>Propionibacterium acne</i>	clinical isolate	WC	<0.125	<0.125	<0.125	<0.125	<0.125
<i>Propionibacterium acne</i>	clinical isolate	WC	<0.125	<0.125	<0.125	<0.125	<0.125
<i>Propionibacterium acne</i>	clinical isolate	WC	<0.125	<0.125	<0.125	<0.125	<0.125

A: Compound of formula (I); B: Compound of Example 10 of US 5,599,791; C: Compound of Example 12 of US 5,599,791; D: Compound of Example 13 of US 5,599,791

The data reported in the above TABLE confirm that all comparison compounds B, C, and D and GE 2270, although presenting the same level of activity of the amide compound of formula (I) of this invention (A) against
5 Propionibacterium acnes strains, they are active also against all Staphylococcus strains tested, with MIC values ranging from 0.06 µg/ml to 8 µg/ml. This activity profile can justify the acknowledgement of a selectivity of action against the Propionibacterium strains.

10 The suitability of the compound of formula (I) for use in the treatment of acne vulgaris has been confirmed in a series of microbiological, toxicological and pharmacokinetic evaluations, the results of which are reported in the following.

15 In TABLE 2 below are summarized the results of a study of the microbiological activity of the amide compound of formula (I) against 15 isolates of P. acnes displaying resistance to clindamycin or erythromycin collected from patients affected by acne. TABLE 3 reports the activity
20 data of the same amide compound of formula (I) against 5 clinical isolates of P. acnes displaying sensitivity toward erythromycin and clindamycin.

TABLE 2

Summary of minimum inhibitory concentration values for erythromycin, clindamycin and compound of formula (I) against clinical isolates of *P. acnes* displaying
 5 antibiotic-resistant phenotypes.

MIC µg/ml	Erythromycin			Clindamycin			Compound of formula (I)		
	N° isolates	Cumul. %	MIC 50/90	N° isolates	Cumul. %	MIC 50/90	N° isolates	Cumul. %	MIC 50/90
0.015									
0.03							9	60%	MIC ₅₀
0.06							6	100%	MIC ₉₀
0.125									
0.25									
0.5									
1									
2									
4				3	20%				
8				2	33%				
16				0					
32				0					
64				8	87%	MIC ₅₀			
128				0					
256				2	100%	MIC ₉₀			
512	1	7%							
1024	11	80%	MIC ₅₀						
2048	3	100%	MIC ₉₀						

TABLE 3

Summary of minimum inhibitory concentration values for erythromycin, clindamycin and compound of formula (I) against clinical isolates of P. acnes displaying antibiotic-sensitive phenotypes

MIC µg/ml	Erythromycin			Clindamycin			Compound of formula (I)		
	N° isolates	Cumul. %	MIC 50/90	N° isolates	Cumul. %	MIC 50/90	N° isolates	Cumul. %	MIC 50/90
0.015									
0.03							4	80%	
0.06							1	100%	
0.125	5	100%	MIC ₉₀	3	60%	MIC ₅₀			
0.25				1	80%				
0.5				1	100%	MIC ₉₀			
1									

15

MIC₅₀ and MIC₉₀ means minimum inhibitory concentration capable of inhibiting 50% and 90%, respectively, of the strains tested.

The above TABLES 2 and 3 shows that the compound of formula (I) is as active against erythromycin and clindamycin resistant P. acne strains as is active against antibiotic sensitive P. acne strains. To determine the frequency of selection of P. acne mutants, resistant to the compound of formula (I), the same compound was incorporated into solid medium at 1 and 10 µg/ml and bacterial suspensions of approximately 10¹⁰ CFU were distributed on the plate surface. Based on the number of grown colonies, the frequency of resistance to the compound of formula (I) ranged from 1.4 X 10⁻⁹ to 1.5 X 10⁻¹⁰ at 1 µg/mL and from 3.3 X 10⁻⁹ to 9.4 X 10⁻¹⁰ at 10 µg/ml.

Dermal administration tests of the compound of formula (I) show that the absorption of the said compound through the skin is very low or null.

Topical absorption was assessed both with the 3% gel formulation of Example 6 below and with a 3% polyethylene glycol 400 solution.

Studies in rabbits with the 3% gel formulation showed measurable plasma concentrations of the test compound after 7 days of daily applications only in a limited number of samples, indicating minimal, if any, absorption. In a 28 days tolerability study on both scarified and non-scarified skin in rabbits, the 3% gel showed no detectable plasma levels throughout the whole study.

According to this invention the compound of formula (I) can be incorporated into a variety of formulations suitable for topical delivery of active ingredients. The topical formulations suitable for topical treatment and prevention of acne vulgaris are creams, lotions, mousses, sprays, emulsions, gels and the like, which are manufactured according to methods commonly known in the art (see, for instance: Topical Formulations: Design and Development - Bozena Michniak/Paperback/CRC Press, LLC/February 1999; Remington: The Science and Practice of Pharmacy 20th - Alfonso L. Gennaro, Alfonso R. (Ed.) Gennaro; Publisher: Lippincott Williams & Wilkins, December 2000, 20th Ed.; Encyclopedia of Pharmaceutical Technology - James Swarbrick (Editor), James C. Boylan (Editor)/Hardcover/Marcel Dekker/May 1997).

In said formulations, the amide derivative of antibiotic GE 2270 of formula (I) may optionally be associated with other components which have auxiliary action in the treatment and prevention of acne or may provide skin benefits. Examples of said additional components are, for instance, other ingredients active against proliferation of Propionibacterium acnes, e.g.

antibiotics such as erythromycin, clindamycin and tetracyclines, antimicrobials such as chlorexidine and benzoylperoxide, synthetic or natural substances which have been described as possessing inhibitory activity against P. acnes such as 1-pentadecanol²⁸⁾ and derivatives thereof²⁹⁾, cedrene, caryophyllene, longifolene and thujopsene³⁰⁾, comedolytic agents such as tretinoin, adapalene, azelaic acid, tazarotene, salicylic acid and derivatives thereof, antiinflammatory agents such as NSAID (e.g. acetylsalicylic acid, ibuprofen, naproxen, sulfacetamide), steroidal antiinflammatory agents (e.g. hydrocortisone), vitamins (e.g. retinoic acid and derivatives thereof), oil or sebum control agents (e.g. clay silicones), skin healing agents, and skin conditioning agents.

In general the amount of the above compound of formula (I) of this invention in the topical composition for treating or preventing acne according to this invention may range from about 0.1% (w/w) to about 10% (w/w).

The topical compositions useful for delivery of the compound of formula (I) contains the usual pharmaceutically acceptable excipients, including those having carrier, vehicle, or other delivery functions, preservative agents, surface active agents, moisture retaining agent, thickeners, perfumes, chelating agents, water, alcohols, antioxidants, antiseptics, colorants and UV adsorbents.

Non limitative examples of topical compositions containing the amide derivative of antibiotic GE 2270 factor A are given herebelow with the purpose of illustrating the invention.

Example 1: 3% cream

	Weight (per cent)
Compound of formula (I), as hydrochloride	3,000
Sodium hydroxide	0,102
Benzyl alcohol	0,850
Sorbitan monostearate	1,615
Cetyl palmitate	1,700
Cetyl alcohol	3,400
Stearyl alcohol	3,400
Polysorbate 60	5,185
Isopropyl myristate	6,800
Diethylene glycol monoethyl ether	12,000
Purified water	61,948
	100,00

Example 2: 3% gel

	Weight (per cent)
Compound of formula (I), as lactate	3,000
Hydroxyethyl cellulose	2,500
Diethylene glycol monoethyl ether	47,000
Purified water	47,000
	100,000

Example 3: 3% alcoholic gel I

	Weight (per cent)
Compound of formula (I), as hydrochloride	3,000
Diethylene glycol monoethyl ether	12,000
Hydroxypropyl cellulose	15,000
Ethyl alcohol 96%	70,000
	100,000

Example 4: 3% alcoholic gel II

	Weight (per cent)
Compound of formula (I)	3,000
Hydroxypropyl cellulose	3,000 or 1,500
Purified water	9,500
Lactic acid	0,500
Ethyl alcohol 95%	84,000 or 85,500
Cetyl alcohol	100,000

5 **Example 5: 3% hydroalcoholic lotion**

	Weight (per cent)
Compound of formula (I)	3,000
Lactic acid	2,000
Diethylene glycol monoethyl ether	36,500
Ethyl alcohol	10,000
Methyl p. hydroxybenzoate	0,150
Propyl p. hydroxybenzoate	0,050
Water	q.s. to 100

Example 6: 1,5% or 3% gel

	Weight (per cent)
Compound of formula (I)	1,500 or 3,000
Methyl cellulose	1,500
Diethylene glycol monoethyl ether	35,000
Ethyl alcohol 96%	10,000
Lactic acid	2,000
Methyl p. hydroxybenzoate	0,150
Propyl p. hydroxybenzoate	0,050
Purified water	q.s. to 100,000

Examples 7, 8 and 9: 0.1%, 1% and 0.5% gels

7)	Weight (per cent)
Compound of formula (I)	0,100
Alcohol SD 40	81,000
Hydroxypropyl cellulose, zinc acetate, propylene glycol, diethylolamine lauramide, fragrances	q.s. to 100,000

5

8)	Weight (per cent)
Compound of formula (I)	1,000
Alcohol SD 40-2	77,000
Propylene glycol, hydroxypropyl cellulose	q.s. to 100,000

	Weight (per cent)
9) Compound of formula (I)	0,500
Butylated hydroxytoluene, hydroxypropyl cellulose, ethyl alcohol	q.s. to 100,000

Example 10: 5% cream

	Weight (per cent)
Compound of formula (I)	5,000
Polyoxyethylene fatty acid esters, cetyl-stearyl octanoate, wax and glycerides mixture, glycol, propylene glycol, benzoic acid, purified water	q.s. to 100,000

5 Example 11: 5% Dermatological suspension

	Weight (per cent)
Compound of formula (I)	5,000
Glycol, isostearyl alcohol, cetyl- stearyl alcohol, stearic acid, glyceryl monostearate, sodium lauroyl sarcosinate, methyl p- hydroxybenzoate, purified water	q.s. to 100,000

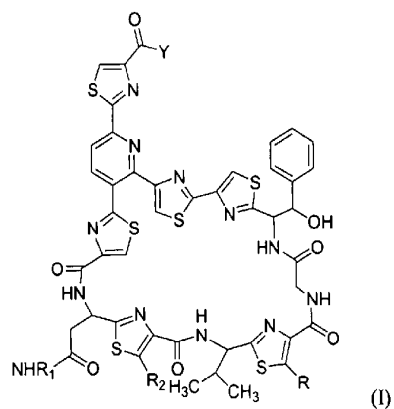
REFERENCES

- ¹⁾ Ebling FJ., Cunliffe WJ. Disorders of sebaceous glands. In: Rook A., Wilkinson DS., Ebling FJ., Champion RH., Burton JL, eds. Textbook of dermatology. Vol III. Boston: Blackwell Scientific, 1992; 1699-744.
- ²⁾ Practitioner 1993; 237:160-164.
- ³⁾ Bergfeld WF, Odom RB. New Perspectives on acne. Clinicians 1996; 12:4.
- ⁴⁾ Cunliffe WJ. The sebaceous gland and acne-40 years on. Dermatology 1998; 9-15.
- ⁵⁾ Leyden JJ. New understanding of the pathogenesis of acne. J Am Acad Dermatol 1995; 32: S15-S25.
- ⁶⁾ Winston MH., Shalita AR. Acne vulgaris: pathogenesis and treatment. Pediatr Clin North Am 1991; 38:889-903.
- ⁷⁾ Webster GF. Inflammation in acne vulgaris. J Am Acad Dermatol 1995; 33:247-253.
- ⁸⁾ Ingham E, Holland KT, Gowland C, et al. Studies of the extracellular proteolytic activity produced by *Propionibacterium acnes*. J Appl Bacteriol 1983; 54:263-271.
- ⁹⁾ Puhvel SM, Sakamoto M. An in vitro evaluation of the inflammatory effect of purified comedonal components in human skin. J Invest Dermatol 1977; 69:401-406.
- ¹⁰⁾ Walters CE, Ingham E, Eady EA, Cove JH, Kearney JN, Cunliffe WJ. In vitro modulation of keratinocyte-derived interleukin-1 alpha (IL-1 alpha) and peripheral blood mononuclear cell-derived IL-1 beta release in response to cutaneous commensal microorganisms. Infect Immun 1995; 63:1223-28.
- ¹¹⁾ Kelly AP. Acne and related disorders. In: Sams JR., Lynch WM., Lynch PJ., eds. Principles and practice of dermatology. 2nd ed. New York, NY: Churchill Livingstone. 1996; 801-808.
- ¹²⁾ Koo JYM, Smith LL. Psychologic aspects of acne. Pediatr Dermatol 1991; 8: 185-88.
- ¹³⁾ Koo J. The psychosocial impact of acne: patients' perceptions. J Am Acad Dermatol 1995; 32: S26-S30.
- ¹⁴⁾ Wu SF, Kinder BN, Trunnel TN, Fulton JE. Role of anxiety and anger in acne patients: a relationship with the severity of the disorder. J Am Acad Dermatol 1988; 18: 325-333.
- ¹⁵⁾ Toyoda M, Murohashi M. An overview of topical antibiotics for acne treatment. Dermatology 1998; 196: 1: 130-4.
- ¹⁶⁾ Berson DS, Shalita AR. The treatment of acne: the role of combination therapies. J Am Acad Dermatol 1995; 32: 531-541.
- ¹⁷⁾ Hurwitz S. The combined effect of vitamin A acid and benzoyl peroxide in the treatment of acne. Cutis 1976; 17: 585-590.
- ¹⁸⁾ Sykes NL, Webster GF. Acne: a review of optimum treatment. Drugs 1994; 48: 59-70.

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- ¹⁹⁾ McEvoy GK, ed. AHFS drug Information. Bethesda, Md: American Society of Health System Pharmacists; 1996.
- ²⁰⁾ Siegle RJ, Fekety R, Sarbone PD, et al. Effects of topical clindamycin on intestinal microflora in patients with acne. *J Am Acad Dermatol* 1986; 15: 180-5.
- ²¹⁾ Crawford WW, Crawford IP, Stoughton RB, Cornell RC. Laboratory induction and clinical occurrence of combined clindamycin and erythromycin resistance in *Corynebacterium acnes*. *J Invest Dermatol* 1979; 72: 187-190.
- ²²⁾ Leyden JJ, McGinley KJ, Cavalieri S et al. *Propionibacterium acnes* resistance in acne patients. *J Am Acad Dermatol* 1983; 8: 41-5.
- ²³⁾ Espersen F. Resistance to antibiotics used in dermatology practice. *Br J Dermatol* 1998; 139 (53): 4-8.
- ²⁴⁾ Eady EA. Bacterial resistance in acne. *Dermatology* 1998; 196:1:59-66.
- ²⁵⁾ Nord CE. Treating acne with antibiotics leads to antibiotic resistance. Proceedings of the 101st Annual Meeting of ASM, Orlando May 2001.
- ²⁶⁾ Ross JJ, Snelling AM, Eady EA, Cove JH, Cunliffe WJ et al. Phenotypic and genotypic characterization of antibiotic-resistant *Propionibacterium acnes* isolated from acne patients attending dermatology clinics in Europe, the U.S.A., Japan and Australia. *Br J Dermatol* 2001; 144: 339-46.
- ²⁷⁾ Eady EA, Cove JH, Holland KT, et al. Erythromycin resistant propionibacteria in antibiotic-treated patients: association with therapeutic failure. *Br J Dermatol* 1989; 121:51-7.
- ²⁸⁾ US 5.380.763
- ²⁹⁾ EP 0577356
- ³⁰⁾ US 5.200.429

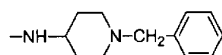
The claims defining the invention are as follows:

1. Use of the compound of formula (I)



wherein:

- 5 R represents methoxymethyl,
 R₁ represents methyl,
 R₂ represents methyl,
 Y represents the group



- 10 and the pharmaceutically acceptable acid addition salts thereof;
for the manufacture of a medicament for the topical treatment or prevention of
acne,
wherein said compound inhibits the growth of *Propionibacterium acnes* strain at
dosages that are inactive against gram-positive bacteria that normally colonize the skin
15 surface.
2. The use according to claim 1, wherein the compound of formula (I) or a
pharmaceutically acceptable acid addition salt thereof is associated with an additional
component that has auxiliary action in the treatment of acne or provides skin benefits.

3. The use according to claim 2, wherein the additional component that has auxiliary action in the treatment of acne or provides skin benefits is selected from the group consisting of an antibiotic, antimicrobial, comedolytic agent, non-steroidal anti-inflammatory agent, steroidal anti-inflammatory agent, vitamin, oil or sebum control agent, skin healing agent, and skin conditioning agent.

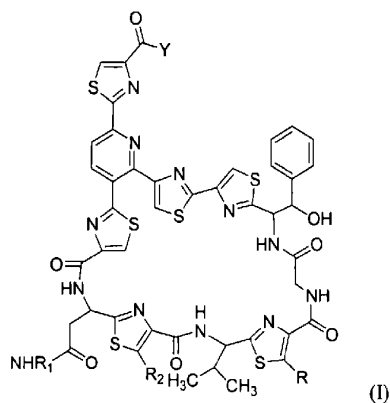
4. The use according to any one of claims 1 to 3, wherein the compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof is incorporated into a pharmaceutical composition suitable for topical administration in an amount ranging from about 0.1 to 10 per cent by weight of said pharmaceutical composition.

5. The use as in any one of claims 1 to 4, wherein the pharmaceutically acceptable acid addition salts are salts with hydrochloric acid or lactic acid.

6. The use as in any one of claims 1 to 5, wherein the gram-positive bacteria that normally colonize the skin surface are selected from the group consisting of *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Staphylococcus pyogenes*.

7. The use as in any one of claims 1 to 6, wherein the gram-positive bacteria that normally colonize the skin surface are resistant to a broader spectrum antibiotic.

8. A medicament for use in the topical treatment or prevention of acne which comprises a compound of formula (I)



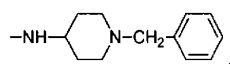
wherein:

R represents methoxymethyl,

R₁ represents methyl,

R₂ represents methyl,

Y represents the group



and the pharmaceutically acceptable acid addition salts thereof, wherein said compound inhibits the growth of *Propionibacterium acnes* strain at dosages that are inactive against gram-positive bacteria that normally colonize the skin surface.

9. The medicament as in claim 8, wherein the compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof is admixed with pharmaceutically acceptable excipients.

10. The medicament as in claim 8 or claim 9, wherein the compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof is contained in an amount which ranges from about 0.1 to 10 percent by weight of the said medicament.

11. The medicament according to any of claims 8 to 10, wherein the medicament is in the form of a cream, lotion, mousse, spray, emulsion or gel.

12. The medicament according to any one of claims 8 to 11, wherein the pharmaceutically acceptable acid addition salts are salts with hydrochloric acid or lactic acid.

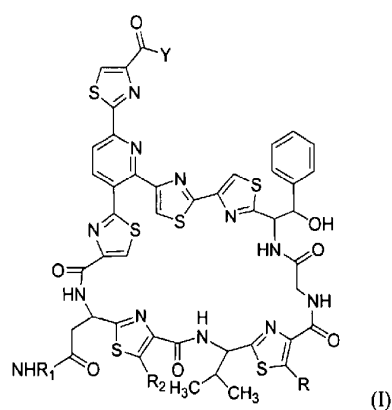
13. The medicament according to any one of claims 8 to 12, further comprising an additional component that has auxiliary action in the treatment of acne or provides skin benefits.

14. The medicament according to claim 13, wherein the additional component that has auxiliary action in the treatment of acne or provides skin benefits is selected from the group consisting of an antibiotic, antimicrobial, comedolytic agent, non-steroidal anti-inflammatory agent, steroidal anti-inflammatory agent, vitamin, oil or sebum control agent, skin healing agent, and skin conditioning agent.

15. The medicament as in any one of claims 8 to 14, wherein the gram-positive bacteria that normally colonize the skin surface are selected from the group consisting of *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Staphylococcus pyogenes*.

16. The medicament as in any one of claims 8 to 15, wherein the gram-positive bacteria that normally colonize the skin surface are resistant to a broader spectrum antibiotic.

17. A method for treating or preventing acne which comprises topically administering a compound of formula (I)



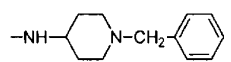
wherein:

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R₁ represents methyl,

R₂ represents methyl,

Y represents the group



or a pharmaceutically acceptable acid addition salt thereof to a patient affected by or exposed to said skin disorder, in an amount sufficient to provide inhibitory activity or proliferation of *Propionibacterium* acne, wherein said compound inhibits the growth of

Propionibacterium acnes strain at dosages that are inactive against gram-positive bacteria that normally colonize the skin surface.

18. The method as in claim 17, wherein the gram-positive bacteria that normally colonize the skin surface are selected from the group consisting of
5 Staphylococcus aureus, Staphylococcus epidermis, and Staphylococcus pyogenes.

19. The method as in claim 17 or claim 18, wherein the gram-positive bacteria that normally colonize the skin surface are resistant to a broader spectrum antibiotic.

20. The method as in claim 17, further comprising the step of administering
10 an additional component that has auxiliary action in the treatment of acne or provides skin benefits.

21. The method as in claim 20, wherein the additional component that has auxiliary action in the treatment of acne or provides skin benefits is selected from the group consisting of an antibiotic, antimicrobial, comedolytic agent, non-steroidal anti-inflammatory agent, steroidal anti-inflammatory agent, vitamin, oil or sebum control agent, skin healing agent, and skin conditioning agent.
15

22. The method as in any one of claims 17 to 21, wherein the compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof is incorporated into a pharmaceutical composition suitable for topical administration in an amount ranging
20 from about 0.1 to 10 per cent by weight of said pharmaceutical composition.

23. The method as in claim 22, wherein the pharmaceutical composition includes a pharmaceutically acceptable excipient.

24. A medicament for use in the topical treatment or prevention of acne which comprises a compound of formula I, substantially as hereinbefore described with
25 reference to any one of the examples.

Dated 23 September, 2009
Vicuron Pharmaceuticals Inc.

Patent Attorneys for the Applicant/Nominated Person
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