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(71) **Applicant**: **PANNONPHARMA GYÓGYSZERGYÁRTÓ ZRT.** [HU/HU]; Mária dűlő 36., H-7634 Pécs (HU).

(72) **Inventors**: **FEISZT, Péter**; Felsővámház u. 51., H-7626 Pécs (HU). **EMŐDY, Levente**; Bajcsy-Zsilinszky Endre u. 33., H-7622 Pécs (HU). **PALLOS, József Péter**; Lomnici u. 33., H-1221 Budapest (HU). **JUHÁSZ, Ákos**; Eper u. 14., H-6000 Kecskemét (HU). **SEFFER, Dénes**; Rákóczi u. 39., H-7720 Pécsvárad (HU). **SEFFERNÉ SZALAI, Mária**; Rákóczi u. 39., H-7720 Pécsvárad (HU). **PÉNZES, Ágota**; Budai Nagy Antal u. 16., H-9600 Sárvár (HU).

(74) **Agent**: **DANUBIA Patent & Law Office LLC**; FEHÉRVÁRI Flóra, Bajcsy-Zs. út 16., H-1051 Budapest (HU).

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(54) **Title**: PRIMYCIN AND COMPONENTS THEREOF FOR USE IN THE TREATMENT OR PREVENTION OF INFECTIONS CAUSED BY SPECIFIC PATHOGENS

(57) **Abstract**: The invention refers to primycin or a primycin component or a combination of primycin components, for use in the treatment or prevention of infections caused by Gram-positive bacteria resistant to methicillin and/or vancomycin and/or mupirocin or by penicillin-resistant streptococci. The invention also covers antibotic compositions containing these active agents.

Primycin and components thereof for use in the treatment or prevention of infections caused by specific pathogens

The invention refers to primycin or a primycin component or a combination of primycin components, for use in the treatment or prevention of infections caused by Gram-positive bacteria resistant to methicillin and/or vancomycin and/or mupirocin or by penicillin-resistant streptococci. The invention also covers antibotic compositions containing these active agents.

Background of the invention

Primycin is a macrolide antibiotic complex comprising more than 20 components, 90% of which consists of nine main components belonging to three major groups.

The first report on primycin was published in 1954 by Vályi-Nagy et al. who isolated the substance from *Streptomyces primycini* cultures [Vályi-Nagy T, Uri J, Szilágyi I. (1954): Nature; 174, 1105.]. Authors report that purified primycin possesses high antibacterial activity against Gram-positive bacteria, namely *Staphylococcus* and *Mycobacterium* species with a minimal inhibitory concentration (MIC) of 0.02 to 0.06 mg/L. According to the paper, primycin is effective against "resistant" strains but the authors do not denominate antimicrobial agents against which these strains are resistant.

In a subsequent study Vályi-Nagy *et al.* report primycin susceptibility of streptomycin--resistant *Mycobacterium* strains [Vályi-Nagy T, Kelentey B. (1960): Arch Int Pharmacodyn Ther 124: 466-481.].

A subsequent publication states that primycin is effective against Gram-negative species with MIC values hundred times higher than those obtained in case of Gram-positives [Horváth I, Kramer M, Bauer PI *et. al.* (1979): Arch Microbiol. 121(2):135-139.]. Authors state this referring unfoundedly to the above *Nature* article (since the latter does not contain such information).

In the same year, a clear denial of previous statement appeared in a publication on the crystallization of primycin [Uri JV, Actor P. (1979): J Antibiot (Tokyo) Nov; 32(11):1207--1209.]. In this paper both crystalline primycin and its amorphous predecessor are reported to be ineffective against Gram-negative species. This article also confirms primycin susceptibility of isolates of *S. aureus* and *Streptococcus faecalis* (i.e. *Enterococcus faecalis* according to the current nomenclature). The MICs reported for these species were in the range of 0.25 to 0.5 μg/ml except for *S. aureus* ATCC 25923 strain, which was not inhibited even at

2 μg/ml, i.e. at the highest primycin concentration tested. The authors found no remarkable difference in the efficacy of amorphous and crystalline primycin.

In a subsequent study [Uri JV. (1986): Acta Microbiol Hung; 33(2):141-146] MIC values for crystalline primycin were measured in media possessing different pH values (i.e. 6, 7.3 and 8, respectively) on large collections of clinical isolates of *S. aureus*, *S. epidermidis*, *E. faecalis* (that time designated as *S. faecalis*) and laboratory strain *Listeria monocytogenes*. All investigated strains were inhibited with MIC values of 0.12 to 0.5 μg/ml, which were only slightly influenced by the actual pH. For laboratory strain *L. monocytogenes* the MIC value of 0.25 μg/ml was measured. The author also stated that the MIC values of primycin were independent of the status of resistance to other antibiotics, however, he did not denominate the latter.

In another publication on the chemical structure of primycin [Frank J, Dékány Gy, Pelczer I, ApSimon W J (1987): Tetrahedron Letters; 28:2759-2762] authors describe primycin as a multicomponent mixture and present the chemical structures of nine main components. They classify primycin in the macrolide antibiotic group.

A review [Nógrádi M. (1988): Drugs of Today 24(8): 563-566] repeats earlier statements according to which primycin is highly effective against Gram-positive bacteria, including "resistant and polyresistant" strains, and in high concentrations, also against Gram--negative bacteria. MIC ranges of primycin for specific genera were summarized as follows: 0.02 to 0.1 mg/L for *Staphylococcus spp.*, *Streptococcus spp.*, *Bacillus spp.*, *Mycobacterium spp.*, *Listeria spp.*, *Sarcina spp.*, *Sporosarcina spp.*, *Propionibacterium spp.*, 1 to 10 mg/L for *Neisseria spp.*, *Enterococcus spp. Vibrio spp.*, 10 to 25 mg/l for *Shigella spp.* and 25 to 50 mg/l for *Pasteurella spp.* and *Serratia spp.*. MIC values of primycin for specific bacterial strains were compared with those of ampicillin, erythromycin, oxytetracycline, streptomycin and clindamycin, as shown in table 1.

Table 1: Efficacy of primycin and reference antibiotics against different bacteria by Nógrádi

Organism	MIC (mg/l)					
	Primycin	Ampicillin	Erythromycin	Oxytetracycline	Streptomycin	Clindamycin
Staphylococcus epidermidis 7586	0.78	<0.5	<0.5	62.5	2.0	31.3
Staphylococcus aureus 7503	0.39	<0.5	>250	1.0	2.0	>250
Diphteroides 8264	50.0	31.3	>250	31.3	>250	250
Staphylococcus saprophyticus 8454	0.39	<0.5	1.0	<0.5	1.0	15.6
Serotype β *Streptococcus* 8252	1.56	<0.5	0.5	1.0	3.9	125
Streptococcus mitis 5728	50.0	7.8	250	1.0	250	>250
Staphylococcus hominis 7835	0.39	<0.5	250	31.3	2.0	31.3
Streptococcus simulans 7866	0.39	<0.5	7.8	2.0	2.0	31.3
Micrococcus spp.	0.78	<0.5	<0.5	7.8	3.9	15.6
Staphylococcus capitis	0.78	<0.5	<0.5	31.3	3.9	31.3
Staphylococcus aureus ATCC 25923	25.0	<0.5	1.0	<0.5	3.9	62.5
Escherichia coli B 1218	50.0	2.0	62.5	1.0	15.6	>250
Enterobacter cloacae B 520	50.0	7.8	250	2.0	7.8	>250
Bacillus subtilis ATCC 6633	0.39	<0.5	<0.5	<0.5	1.0	15.6
Propionibacterium acnes	<0.1	1.0	<0.5	<0.5	<0.5	0.5

This review cited another study [Nógrádi M. (1988): Drugs of Today 24(8): 563-566] according to which 1% of a collection of 279 erythromycin-sensitive *Staphylococcus spp.* strains was primycin-resistant (MIC≥5 mg/L), while 13% of 71 erythromycin-resistant staphylococci presented primycin resistance.

In a handbook [Bryskier A. (2005) ASM Press Washington DC: Antimicrobials – antibacterials and antifungals, chapter titled "Primycin", pages 1179-1180] primycin is characterized as being effective against *S. aureus* and coagulase-negative staphylococci but showing only moderate efficacy against enterococci and *S. pyogenes*. The author mentions that primycin is effective against *Bacillus spp.* and *Micrococcus spp.*, but ineffective against *Corynebacterium spp.*, *Enterobacteriaceae* species, *Pseudomonas aeruginosa*, yeasts and dermatophytes. The author presents a table which partly overlaps with the one included in the cited Nógrádi article, see table 2.

Table 2: Efficacy of primycin and reference antibiotics against different bacteria by Bryskier

Organism(s)	MIC (mg/l)				
	Primycin	Ampicillin	Erythromycin A	Tetracycline	Clindamycin
S. aureus	0.39	<0.5	>250	1.0	>250
S. aureus ATCC 25923	25	<0.5	1.0	<0.5	62.5
Staphylococcus epidermidis	0.78	<0.5	<0.5	62.5	31.3
S. pyogenes	1.56	<0.5	0.5	1.0	125
Streptococcus mitis	50	7.8	250	1.0	>250
Micrococcus	0.78	<0.5	<0.5	7.8	15.6
Coryneform(s)	50	31.3	>250	31.3	250
B. subtilis ATCC 6633	0.39	<0.5	<0.5	<0.5	15.6
Escherichia coli	50	2.0	62.5	1.0	>250
Enterobacter cloacae	50	7.8	250	2.0	>250
Propionibacterium acnes	<0.1	1.0	<0.5	<0.5	0.5

Hungarian Patent No. 153593 (Owner: Chinoin Gyógyszer és Vegyészeti Termékek Gyára Rt., Budapest) describes an improved process for the preparation of primycin. This patent concerns an industrial-scale process utilizing a *Thermopolyspora galeriensis* strain, by which primycin can be produced more effectively. Antibiotic-producing properties of the new industrial strain surpass those of the *Streptomyces primycini* strains used previously for this purpose.

Hungarian Patents Nos. 195514, 196309 and 196822 (Owner for each: Chinoin Gyógyszer és Vegyészeti Termékek Gyára RT, Budapest) disclose information on microbial pathogens against which primycin is applicable. In each document it is declared in general that primycin is effective primarily against Gram-positive pathogens.

Hungarian Patent No. 196309 describes synergistic effect of dual or triple combinations of primycin components A1, B1 and C1 in various mass ratios. The antimicrobial effect of the individual primycin components is also described, which proves their independent applicability.

US Patent No. US4873348 discloses nine components of primycin and describe the outstanding efficacy of oxypricin (primycin component C1).

Summary of Product Characteristics of Ebrimycin gel, a human medicinal product containing primycin as active substance, includes the following statement: Based on literary data, synergistic interaction is present in dual or multiple combinations of primycin with agents selected from the group of oxytetracycline, streptomycin and oxacillin, or from penicillin and vancomycin. Antagonistic interaction of primycin is reported with novobiocin, erythromycin, chloramphenicol, fuzidine.

Synergistic interactions of primycin with other antibiotics are described in the following documents as well.

According to US Patent No. US3949077 primycin shows synergistic effect in dual combination with viomycin, streptomycin, oxacillin, neomycin or oxytetracycline or in triple combination with neomycin and oxytetracycline.

US Patent No. US4404189 discloses synergistic combinations of primycin with sisomicin and/or doxycyclin.

The problem to be solved by the invention

Antibiotic resistance is an emerging problem in the therapy of bacterial infections. Resistance against widely used antibiotics is already so frequent that new therapy protocols have to be elaborated for patients affected.

The scientific literare on the applicability of primycin is rather incomplete, still it suggests that primycin is efficient primarily against Gram-positive pathogens, particularly against *Staphylococcus* species.

According to the above cited Hungarian Patents Nos. 195514, 196309 and 196822 primycin is also active against polyresistant strains. However the credibility of this statement cannot be verified; the antibiotics to which these bacterial strains show resistancy were not specified, moreover some of the strains titled in these patents as being polyresistant are no longer available (i.e. no information is available concerning their "polyresistance"). Even a strain that was not polyresistant at the filing date of these patents was mentioned, as seen in table 3. It can be stated however, that these strains cannot be characterized by the antibiotic resistances discussed in the present description.

Furthermore, the presently studied Gram-positive bacterial strain *Streptococcus pneumoniae* was not mentioned in the above patents.

Table 3: Gram-positive bacterial strains titled as polyresistant in the patent literature on the efficacy of primycin

Bacterial strains titled as polyresistant in earlier patents		**Note**
Species	**Strain id. number**	
Bacillus subtilis	ATCC 6633	Not polyresistant. A strain often used to estimate the efficacy of antibiotics.
Bacillus subtilis	CCM 1718, ATCC 9799	Not resistant against methicillin, mupirocin or vancomycin. Polyresistance is not confirmed.
Bacillus cereus	CCM 2010, ATCC 14579	
Bacillus licheniformis	CCM 2182	
Bacillus licheniformis	CCM 2205, ATCC 9789	
Listeria monocytogenes	CCM 5576, ATCC 19111	
Micrococcus luteus	DSM 20030, ATCC 4698	
Sporosarcina ureae	DSM 317	
Staphylococcus aureus	CCM 885, ATCC 12600	
Staphylococcus aureus	CCM 2317	
Staphylococcus aureus	CCM 2514	Not available.

Bacterial strains titled as polyresistant in earlier patents		Note
Species	**Strain id. number**	
Staphylococcus aureus	CCM 2326	Methicillin-, mupirocin- or vancomycin-resistance is not present. Polyresistance is not confirmed.
Staphylococcus aureus	CCM 2515	
Staphylococcus epidermidis	CCM 2271	Not available.
Staphylococcus aureus	Smith ATCC 12715, 19636	Methicillin-, mupirocin- or vancomycin-resistance is not present. Polyresistance is not confirmed.
Staphylococcus aureus	DSM 20231, ATCC 12600	
Streptococcus faecalis	CCM 1875, ATCC 11700	
Streptococcus agalactiae	CCM 5534	
Streptococcus agalactiae	CCM 5153	
Streptococcus disgalactiae	CCM 5548, ATCC 9026	
Streptococcus disgalactiae	ATCC 9926	
Micrococcus flavus	ATCC 10240	

The purpose of our work was to reveal yet unknown application opportunities of primycin, primarily against well-characterized pathogen groups with specified antibiotic resistance causing significant difficulties in the therapy. The primycin susceptibility of these pathogen groups and thus, the applicability of primycin against them have not been described until now.

Presently, the following strains cause the most and major problems in the therapy: methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (MRCoNS), vancomycin-resistant enterococci (VRE), vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus* (VISA and VRSA), the latter strains possess methicillin-resistance as well. To eradicate asymptomytic MRSA/VISA/VRSA-colonization of the hospital staff, Mupirocin is usually used, which resulted in selection of mupirocin-

-resistant variations of these pathogens. The afore-mentioned resistances are often accompanied by cross-resistances to several agents, including macrolide antibiotics and thus theoretically to primycin as well. This theory is supported by the fact that, while earlier publications did not mention primycin-resistance, the above cited paper by Nógrádi (1988) reported that 1% of a collection of 279 erythromycin-sensitive *Staphylococcus spp.* strains was primycin-resistant (MIC≥5 mg/L), while 13% of 71 erythromycin-resistant staphylococci presented primycin resistance, which indicates a connection between erythromycin- and primycin-resistance.

In addition, primycin resistance appeared in case of *Staphylococcus aureus* ATCC 25923 strain, according to earlier publications. In view of the fact that primycin has been on the market since the issuance of the papers that already mentioned primycin-resistant strains, there has been a chance for selection and spreading of primycin-resistant strains.

Besides those mentioned above, currently upcoming *Streptococcus pneumoniae* strains with decreased penicillin susceptibility or penicillin-resistance are also of great clinical importance.

In respect of the adequate therapy and the related clinical outcome, patients with infections caused by bacteria possessing the above-described resistance(s) constitute patient groups clearly separated from those infected by susceptible strains of the same species.

By testing the primycin-susceptibility of bacteria possessing the above-described resistance(s) it can be decided whether these strains show cross-resistance to primycin. If not, primycin can afford new opportunity in therapy and prevention of infections caused by these bacteria.

General description of the invention

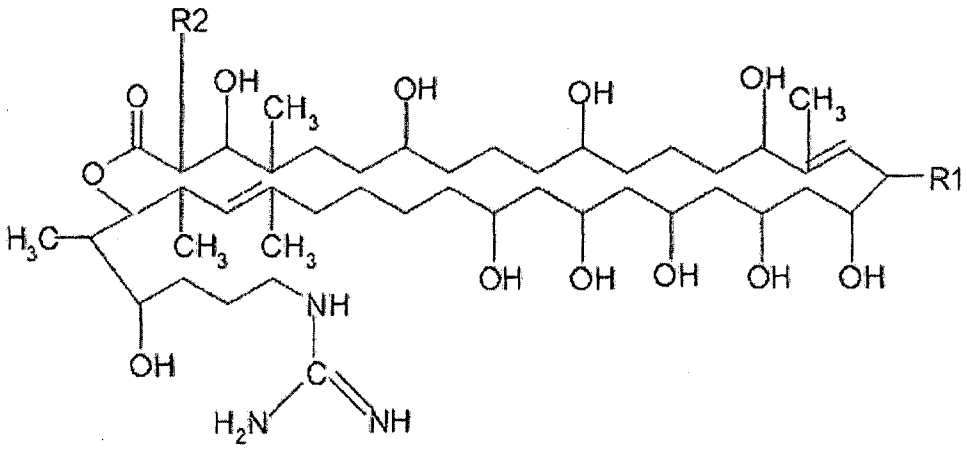
The invention relates to primycin or a primycin component or a combination of primycin components for use in the treatment or prevention of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococcus spp.* (MRCoNS), vancomycin-intermediate or vancomycin-resistant *Staphylococcus aureus* (VISA, VRSA), mupirocin-resistant *Staphylococcus spp.*, vancomycin-resistant *Enterococcus spp.* (VRE) or penicillin-resistant *Streptococcus pneumoniae* strains.

The invention covers pharmaceutical compositions containing primycin or a primycin component or a combination thereof for use in the treatment or prevention of infections caused by the bacterial strains defined above.

The invention also covers antibiotic compositions containing primycin or a primycin component or a combination thereof for use in the treatment or prevention of infections caused by the bacterial strains defined above.

Detailed description of the invention

Primycin components for use according to the invention are represented by general formula (I):



wherein R1 is n-butyl, n-pentyl or n-hexyl and R2 is arabinosyl, H or OH.

Said primycin components are in basic form or in salt form. Among them preferred are sulphate salts, but they can form salts with other inorganic or organic acids, such as acetate.

Denominations and substituents R1 and R2 of the primycin components of formula (I) are as follows:

Component	R1	R2
A1 (chinopricin)	n-butyl	-arabinosyl
A2 (midopricin)	n-pentyl	-arabinosyl
A3 (metipricin)	n-hexyl	-arabinosyl
B1 (hydropricin)	n-butyl	-H
B2 (hymipricin)	n-pentyl	-H
B3 (hymetipricin)	n-hexyl	-H
C1 (oxypricin)	n-butyl	-OH
C2 (oxymipricin)	n-pentyl	-OH
C3 (oxymetipricin)	n-hexyl	-OH

The chemical name of primycin component A1 is for example 18-arabinosyl-2-butyl--3,7,11,15,19,21,23,25,27,37-decahydroxy-4,16,32,34,36-pentamethyl-tetraconta-16,32--diene-35-O-lacton-40-guanidin-sulphate or {5-/19-(α-D-Arabinofuranosyloxy)-35-butyl--10,12,14,16,18,22,26,30,34-nonahydroxy-3,5,21,33-tetramethyl-36--oxooxacyclohexatriaconta-4,40-diene-2-il/-4-hydroxyhexyl}-guanidin-sulphate.

The term "combination of primycin components" used in the present description refers to a mixture of at least two primycin components in any ratio.

In one embodiment, the invention relates to combination of primycin components A1 and B1 in a ratio of 1:3 to 3:1, for example 1:3, 1:1 or 3:1 (molar ratios).

In another embodiment, the invention relates to combination of primycin components A1 and C1 in a ratio of 1:3 to 3:1, for example 1:3, 1:1 or 3:1.

In another embodiment, the invention relates to combination of primycin components C1 and B1 in a ratio of 1:3 to 3:1, for example 1:3, 1:1 or 3:1.

In another embodiment, the invention relates to combination of primycin components A1, B1 and C1 in a ratio of 4:3:3 to 7:2:1, for example 4:3:3, 5:2.5, 6:2:2 or 7:2:1.

Primycin for use according to the present invention can be manufactured via the process described in the above Hungarian Patent No. 153593 (Chinoin). The primycin components can be prepared by the processes described in Hungarian Patents Nos. 195514 (published as T/39186) and 196425 (published as T/39187). Full contents of these patents are incorporated in the present description by reference.

The pharmaceutical composition according to the invention contains as active agent primycin or a primycin compound or a composition of primycin compounds together with at least one pharmaceutical acceptable carrier or additive.

The term "pharmaceutical composition" used in the present description refers to any composition containing together with carriers and/or additives, an active agent useable for retaining or recovering health of a human or an animal, independently of the way of administration, including dietary supplements, functioned food nutraceutical food and the like.

The pharmaceutical compositions according to the invention can be in any commonly used forms, for example solid, semisolid or liquid forms and contain commonly used excipients and/or vehicle materials determined by the given form.

Solid pharmaceutical forms can be for example tablets, capsules or coated tablets, semisolid forms can be ointments, creams or gels, liquid forms can be solutions, suspensions or emulsions.

Solid forms, like tablets capsules or coated tablets can be administered orally. Further oral preparations are liquid compositions like solutions, suspensions or emulsions. Powder mixtures added to forage or solutions added to drinking water can be used for veterinary applications.

Parenterally applicable pharmaceutical forms are aqueous solutions, suspensions or emulsions.

Topically or locally applicable forms are powders, ointments, gels or aqueous solutions, suspensions or emulsions. Semisolid and liquid forms are preferably used on the surfaces of mucous membranes.

The pharmaceutical compositions are prepared by mixing the active substance with non--toxic, inert vehicles and/or excipients commonly used in pharmaceutics.

Conventionelly used vehicle materials are for example water, gelatine, lactose, starch, magnesium-stearate, stearic acid, glycols, alcohols, vegetable oils, etc. In case of creams and ointments vaseline, liquid paraffin, lanoline, polyethylene-glycols, alcohols and any mixtures thereof can be used as vehicles. Excipients conventionally used in pharmaceutics are for example preservatives, buffers, moisturizers, emulsifiers, colorants, flavorings, etc.

The pharmaceutical compositions exemplified above and preparations thereof are well known e.g. from the Remington's Pharmaceutical Sciences manual [18. issue, Mack Publishing Co., Easton, USA (1990)].

The pharmaceutical compositions according to the invention are preferably applied on the surfaces of skin or mucous membrane. Advantageously, they are in the forms of creams, ointments, gels, solutions or aqueous suspensions, the latter are preferably in the forms of eye drops, nasal drops or nasal spray, lotion, and can contain commonly used vehicles and/or excipients adequate to the given form.

The pharmaceutical compositions according to the invention contain primycin or a primycin component or a combination of primycin components in an amount adequate to the specific form, the way of administration, and the MIC value of the target microorganism.

The topically applicable pharmaceutical compositions according to the invention contain primycin or a primycin component or a combination of primycin components preferably in a concentration range of 0.01 to 10 mg/g, more preferably of 0.1 to 1.0 mg/g.

An aqueous suspension applicable on mucous membranes contains preferably 50 to 150 mg/g of polyvinyl alcohol, 0.2 to 1.2 mg/g of anhydrous NaH_2PO_4, 4.0 to 5.0 mg/g of $Na_2HPO_4.2H_2O$, 6 to 7 mg/g of polysorbate, 1.0 to 1.5 mg/g of disodium edetate, 5.0 to 6.0 mg/g of sodium chloride and water for injection.

An alcoholic gel according to the invention preferably contains 7.0 to 14 mg/g of carbomera, 15 to 20 mg/g of triethanolamine, 15 to 20 mg/g of polysorbate, 50 to 70 mg/g of isoadipate, 400 to 600 mg/g ethanol (96%) and purified water.

Compositions applicable on the surfaces of mucous membrane can be used for example to eradicate asymptomatic methicillin- and/or vancomycin- and/or mupirocin-resistant nasal colonisations of the hospital personnel. In this manner, the personnel cease to be an infection source.

The term "antibacterial composition" used in the present description refers to any composition containing primycin or a primycin component or a combination of primycin components for use according to the present invention, together with carriers and/or vehicles commonly used in sanitary and hygienic products. The forms and concentration ranges of these compositions are as described for pharmaceutical compositions above.

Bacteriological studies

The research work during which the present invention was elaborated, was carried out in the Department of Medical Microbiology and Immunology, Medical School, University of Pécs.

Susceptibilities of a total of 105 clinical isolates of genera *Staphylococcus, Streptococcus* and *Enterococcus* and 11 international reference strains were tested to primycin, vancomycin, gentamicin, erythromycin, tobramycin, neomycin, ofloxacin, and oxytetracyclin. Identification and characterization of resistance patterns of these bacteria were performed by standard methods.

When forming the test groups we attached great importance to the increasing incidence of drug-resistant microbes causing therapeutic problems. Most important of them are methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococcus spp.* (MRCoNS), penicillin-resistant *Streptococcus pneumoniae* (pneumococcus), vancomycin-resistant *Enterococcus spp.* (VRE). Pneumococcus isolates represented various serotypes, VRE isolates belonged to various species. Moreover, vancomycin-resistance of VRE isolates was based on different genetic backgrounds. Antibiotic-resistant strains were also represented among international reference strains, for example methicillin-resistant *Staphylococcus aureus* ATCC 43300 (MRSA), *Staphylococcus aureus* with decreased vancomycin susceptibility ATCC 700698 and 700699 (vancomycin intermediate *Staphylococcus aureus* – VISA), mupirocin-resistant *Staphylococcus aureus* ATCC BAA1708 and vancomycin-resistant *Enterococcus faecalis* ATCC 51299 (VRE).

Susceptibility tests were performed according to the standard microdilution method (NCCLS (CLSI) M7-A7).

Efficacy of antibiotics was tested at concentrations presented in Table 4.

Table 4: Antibiotic concentrations tested (**sensitive MIC range**, *intermediate range*, resistant range).

Test agents	Final concentrations tested (mg/L)									
Primycin	8	4	2	1	0.5	0.25	0.12	0.06	0.03	0.015
Ofloxacin	16	8	*4*	2	1	0.5	0.25	0.12	0.06	0.03
Tobramycin	32	16	*8*	4	2	1	0.5	0.25	0.12	0,06
Oxytetracycline	32	16	*8*	4	2	1	0.5	0.25	0.12	0.06
Erythromycin	16	8	4	*2*	*1*	0.5	0.25	0,12	0.06	0.03
Gentamicin	16	8	4	2	1	0.5	0.25	0.12	0.06	0.03
Neomycin	32	16	8	4	2	1	0.5	0.25	0.12	0.06
Vancomycin	32	16	*8*	4	2	1	0.5	0.25	0.12	0.06

The lowest concentration at which no bacterial growth was observed after the incubation period is the Minimal Inhibitory Concentration (MIC). The MIC value is inversely proportional to the antimicrobial efficacy. MIC values of antimicrobial agents can differ by species or even by bacterial strains within species. MIC_{50} and MIC_{90} values (the lowest concentrations inhibiting 50 or 90%, respectively, of the isolates) were calculated from a minimum of 10 strains of a microbe group formed according to objective aspects.

The concentration ranges of reference antimicrobial agents tested parallel with primycin were selected to involve the MIC interpretive breakpoints reflecting the clinical applicability (Table 4).

Susceptibilities of bacterial strains and groups thereof to vancomycin, gentamicin, erythromycin, tobramycin, neomycin, ofloxacin and oxytetracycline were in good correlation with literary data (Table 5). Among these agents only vancomycin showed high and extended efficacy.

Resistance patterns of MRSA, MRCoNS and VRE isolates show decreased susceptibility to the reference antibiotics, including erythromycin, which belongs to the macrolide antibiotic group. As it was expected, methicillin- and vancomycin-resistance often coexistes with resistance to the other antibiotics.

We have surprisingly found that primycin inhibited all the tested bacteria with MIC_{90}

values of 0.06 to 1 mg/L depending on species, including MRSA, MRCoNS and VRE isolates. Surprisingly, no cross-resistance to primycin appeared with methicillin-resistance or with vancomycin-resistance, despite the fact that primycin belongs to the macrolide group. Cross-resistance to primycin was not experienced among erythromycin-resistant isolates either, as it can be seen in table 5.

Table 5: Efficacy of primycin and comparative agents against clinical isolates of Gram-positive bacteria

Antimicrobials	Bacteria (number of isolates)	MIC (mg/L)			Ratio of Sensitive/Total
		Range	50%	90%	
Primycin	*Staphylococcus aureus*, methicillin susceptible (10)	0.06 – 0.06	0.06	0.06	10/10
	Staphylococcus aureus, methicillin resistant (10)	0.06 – 0.06	0.06	0.06	10/10
	Coagulase-negative *Staphylococus sp.*, methicillin susceptible (10)	0.03 – 0.06	0.03	0.06	10/10
	Coagulase-negative *Staphylococus sp.*, methicillin resistant (10)	0.03 – 0.06	0.06	0.06	10/10
	Enterococcus sp., vancomycin susceptible (20)	0.5 - 1	0.5	0.5	20/20
	Enterococcus sp., decreased vancomycin susceptibility (5)	0.25 – 0.5	-	-	5/5
	Streptococcus pneumoniae, penicillin susceptible (10)	0.25 - 1	0.5	0.5	10/10
	Streptococcus pneumoniae, penicillin resistant (10)	0.5 - 1	0.5	1	10/10
	Streptococcus viridans sp. (20)	0.5 - 1	1	1	20/20
Vancomycin	*Staphylococcus aureus*, methicillin susceptible (10)	0.5 - 2	1	1	10/10
	Staphylococcus aureus, methicillin resistant (10)	0.5 - 1	1	1	10/10
	Coagulase-negative *Staphylococus sp.*, methicillin susceptible (10)	1 - 2	1	2	10/10
	Coagulase-negative *Staphylococus sp.*, methicillin resistant (10)	1 - 2	2	2	10/10
	Enterococcus sp., vancomycin susceptible (20)	1 - 4	1	2	20/20
	Enterococcus sp., decreased vancomycin susceptibility (5)	8 - >32	-	-	0/5
	Streptococcus pneumoniae, penicillin susceptible (10)	0.25 – 0.5	0.5	0.5	10/10
	Streptococcus pneumoniae, penicillin resistant (10)	0.25 – 0.5	0.5	0.5	10/10
	Streptococcus viridans sp. (20)	0.5 - 1	0.5	1	10/20

WO 2013/061101 PCT/HU2012/000111

Table 5 cont.					
Gentamicin	*Staphylococcus aureus*, methicillin susceptible (10)	0.25 - 0,5	0.5	0.5	10/10
	Staphylococcus aureus, methicillin resistant (10)	0.25 - 1	0.5	0.5	10/10
	Coagulase-negative *Staphylococus sp.*, methicillin susceptible (10)	0.03 - 8	0.125	4	9/10
	Coagulase-negative *Staphylococus sp.*, methicillin resistant (10)	0.06 - >16	0.125	>16	6/10
	Enterococcus sp., vancomycin susceptible (20)	4 - >16	8	>16	1/20
	Enterococcus sp., decreased vancomycin susceptibility (5)	8 - 16	-	-	0/5
	Streptococcus pneumoniae, penicillin susceptible (10)	8 - 16	16	16	0/10
	Streptococcus pneumoniae, penicillin resistant (10)	8 - >16	16	>16	0/10
	Streptococcus viridans sp. (20)	2 - >16	8	16	9/20
Erythromycin	*Staphylococcus aureus*, methicillin susceptible (10)	0.125 - >16	0.125	>16	7/10
	Staphylococcus aureus, methicillin resistant (10)	0.25 - >16	>16	>16	1/10
	Coagulase-negative *Staphylococus sp.*, methicillin susceptible (10)	0.03 - >16	0.125	>16	8/10
	Coagulase-negative *Staphylococus sp.*, methicillin resistant (10)	0.125 - >16	0.25	>16	5/10
	Enterococcus sp., vancomycin susceptible (20)	0.03 - >16	1	>16	13/20
	Enterococcus sp., decreased vancomycin susceptibility (5)	0.06 - >16	-	-	2/5
	Streptococcus pneumoniae, penicillin susceptible (10)	0.03 - >16	0.03	0.03	9/10
	Streptococcus pneumoniae, penicillin resistant (10)	0.03 - >16	2	>16	2/10
	Streptococcus viridans sp. (20)	0.03 - >16	1	>16	10/20

WO 2013/061101 PCT/HU2012/000111
16

Table 5 cont.					
Oxytetracyclin	*Staphylococcus aureus*, methicillin susceptible (10)	0.25 - 32	0.25	32	8/10
	Staphylococcus aureus, methicillin resistant (10)	0.125 – 0.25	0.25	0.25	10/10
	Coagulase-negative *Staphylococus sp.*, methicillin susceptible (10)	0.125 - >32	0.25	1	9/10
	Coagulase-negative *Staphylococus sp.*, methicillin resistant (10)	0.125 - >32	1	>32	8/10
	Enterococcus sp., vancomycin susceptible (20)	0.25 - >32	16	32	6/20
	Enterococcus sp., decreased vancomycin susceptibility (5)	0.25 - 16	-	-	2/5
	Streptococcus pneumoniae, penicillin susceptible (10)	1 -8	1	8	8/10
	Streptococcus pneumoniae, penicillin resistant (10)	4 - >32	32	>32	1/10
	Streptococcus viridans sp. (20)	1 - >32	4	>32	10/20
Tobramycin	*Staphylococcus aureus*, methicillin susceptible (10)	0.5 - 1	0.5	0.5	10/10
	Staphylococcus aureus, methicillin resistant (10)	0.5 - >32	1	>32	6/10
	Coagulase-negative *Staphylococus sp.*, methicillin susceptible (10)	0.06 - 4	0.06	4	10/10
	Coagulase-negative *Staphylococus sp.*, methicillin resistant (10)	0.06 - >32	0.06	>32	5/10
	Enterococcus sp., vancomycin susceptible (20)	8 - >32	16	>32	0/20
	Enterococcus sp., decreased vancomycin susceptibility (5)	8 - >32	-	-	0/5
	Streptococcus pneumoniae, penicillin susceptible (10)	16 - 32	16	32	0/10
	Streptococcus pneumoniae, penicillin resistant (10)	16 - >32	32	>32	0/10
	Streptococcus viridans sp. (20)	4 - 32	16	32	1/20

WO 2013/061101 PCT/HU2012/000111
17

Table 5 cont.					
Neomycin	*Staphylococcus aureus*, methicillin susceptible (10)	0.5 - 2	1	2	10/10
	Staphylococcus aureus, methicillin resistant (10)	0.5 - >32	1	>32	5/10
	Coagulase-negative *Staphylococus sp.*, methicillin susceptible (10)	0.06 - 4	0.25	1	10/10
	Coagulase-negative *Staphylococus sp.*, methicillin resistant (10)	0.06 - >32	0.25	16	8/10
	Enterococcus sp., vancomycin susceptible (20)	16 - >32	>32	>32	0/20
	Enterococcus sp., decreased vancomycin susceptibility (5)	16 - >32	-	-	0/5
	Streptococcus pneumoniae, penicillin susceptible (10)	32 - >32	>32	>32	0/10
	Streptococcus pneumoniae, penicillin resistant (10)	>32 - >32	>32	>32	0/10
	Streptococcus viridans sp. (20)	16 - >32	>32	>32	0/20
Ofloxacin	*Staphylococcus aureus*, methicillin susceptible (10)	0.5 - 1	0.5	1	10/10
	Staphylococcus aureus, methicillin resistant (10)	1 - >16	16	>16	1/10
	Coagulase-negative *Staphylococus sp.*, methicillin susceptible (10)	0.25 - 1	1	1	10/10
	Coagulase-negative *Staphylococus sp.*, methicillin resistant (10)	4 - >16	>16	>16	0/10
	Enterococcus sp., vancomycin susceptible (20)	2 - >16	4	>16	3/20
	Enterococcus sp., decreased vancomycin susceptibility (5)	2 - 8	-	-	2/5
	Streptococcus pneumoniae, penicillin susceptible (10)	1 - 4	2	2	9/10
	Streptococcus pneumoniae, penicillin resistant (10)	1 - 2	1	2	10/10
	Streptococcus viridans sp. (20)	1 - 8	2	4	14/20

WO 2013/061101 PCT/HU2012/000111
18

Neither the serotype nor the degree of the penicillin susceptibility of *S. pneumoniae* strains influenced the excellent efficacy of primycin, as seen in table 6.

Table 6: Pimycin susceptibilities of 20 *S. pneumoniae* isolates of various serotypes and penicillin susceptibility

Penicillin susceptible *S. pneumoniae*			**Penicillin resistant *S. pneumoniae***		
Serotype	**MIC (mg/L)**		**Serotype**	**MIC (mg/L)**	
	Penicillin	**Primycin**		**Penicillin**	**Primycin**
19F	0.03	0.5	19A	16	0.5
9(V)	0.03	0.5	19A	8	1
23(F)	0.015	0.25	19A	4	0.5
4	0.015	0.5	19A	4	1
8	0.015	0.5	19A	4	0.5
3	0.015	0.5	14	4	0.5
7F	0.015	0.5	14	2	0.5
11(A)	0.06	0.5	14	2	0.5
6(A)	0.06	1	14	2	0.5
6(A)	0.015	0.5	23(F)	2	0.5

Neither the species, nor the degree of the vancomycin-resistance or the type of the resistance gene of vancomycin-resistant enterococci affected the excellent efficacy of primycin, as seen in table 7.

Table 7: Primycin susceptibilities of *Enterococcus* isolates with various *van* resistance genes

Species	**Resistance gene**	**MIC (mg/L)**	
		Vancomycin	**Primycin**
E. faecalis	*van* A	>32	0.5
E. faecalis	*van* C1	8	0.5
E. faecium	*van* B	>32	0.25
E. casseliflavus	*van* C1	16	0.5
E. casseliflavus	*van* C2	8	0.5

The primycin susceptibilities of ATCC reference strains showed good accord with the susceptibilities of the clinical isolates.

Reference strains *S. aureus* ATCC 43300 (MRSA), *S. aureus* ATCC 700698, and 700699 (VISA), *S. aureus* ATCC BAA1708 (mupirocin-resistant), *E. faecalis* ATCC 51299 (VRE) also proved to be sensitive to primycin to the same extent as it was observed with clinical isolates, as it can be seen in table 8.

Table 8: Antibacterial activity of primycin against ATCC reference strains

Species	Strain	Resistance	Primycin MIC (mg/l)
Staphylococcus aureus	ATCC 29213		0.06
Staphylococcus aureus	ATCC 25923		0.06
Staphylococcus aureus	ATCC 43300	MRSA	0.06
Staphylococcus aureus	ATCC 700698	VISA	0.06
Staphylococcus aureus	ATCC 700699	VISA	0.125
Staphylococcus aureus	ATCC BAA1708	mupirocin-resistant	0.06
Enterococcus faecalis	ATCC 29212		0.5
Enterococcus faecalis	ATCC 51299	VRE	1
Streptococcus	ATCC 49619		0.5
Enterococcus hirae	ATCC 8043		0.5
Bacillus subtilis	ATCC 6633		0.03
Escherichia coli	ATCC 25922		>64

Taken all together, excellent efficacy of primycin was observed against all the bacteria tested, and this efficacy was not affected by any resistances to any tested antibiotics or by the mechanisms of said resitances.

Based on the facts above it can be established that primycin can be applied excellently against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase--negative *Staphylococcus sp.* (MRCoNS), vancomycin-intermediate of vancomycin-resistant *Staphylococcus aureus* (VISA, VRSA), mupirocin-resistant *Staphylococcus sp.*, vancomycin--resistant *Enterococcus sp.* (VRE) and penicillin-resistant *Streptococcus pneumoniae* strains.

Examples:

Example 1

Ointment containing primycin as active substance applicable on the surfaces of skin or mucous membrane

Composition:

Primycin	1.0 mg/g
White vaseline	700 mg/g
Wool fat	50 mg/g
Liquid paraffin	300 mg/g

Preparation:

Primycin is suspended in liquid paraffin at 60-65°C. White vaseline and wool fat are separately warmed to 60-65°C. The two solutions are homogenized and cooled to 35-40°C with continuous stirring.

Example 2

Other ointment compositions applicable on the surfaces of skin or mucous membrane

These ointments are prepared according to the procedure described in example 1 applying one of the following active ingredients in the following concentration ranges.

Composition:

Primycin or Primycin component or Combination of primycin components	0.01 – 10.0 mg/g
White vaseline	600-800 mg/g
Wool fat	50-60 mg/g
Liquid paraffin	200-400 mg/g

Example 3

Aqueous suspensions containing primycin as active substance, applicable on the surfaces of skin or mucous membrane

Composition:

Primycin	0.5 mg/g
Poly(vinyl-alcohol)	100 mg/g

NaH_2PO_4 . 0 H_2O	0.5 mg/g
Na_2HPO_4 . 2 H_2O	4.5 mg/g
Polysorbate	6.0 mg/g
Disodium edetate	1.0 mg/g
Sodium chloride	5.0 mg/g
Water for injection	ad 1000 g

Preparation:

1. Sodium dihydrogen phosphate is dissolved in water for injection, with stirring.
2. Disodium hydrogen phosphate is dissolved in the stirred solution.
3. Sodium chloride is dissolved in the stirred solution.
4. Disodium edetate is dissolved in the stirred solution.
5. Polysorbate is mixed with continuous stirring and the solution is adjusted with water for injection.
6. The active ingredient is suspended in the mixture with continuous, intensive stirring.

Example 4

Other aqueous suspensions applicable on the surfaces of skin or mucous membrane

These suspensions are prepared according to the procedure described in example 3 applying one of the following active ingredients in the following concentration ranges.

Composition:

Primycin or	
Primycin component or	
Combination of primycin components	0.01 – 10.0 mg/g
Poly(vinyl-alcohol)	50-150 mg/g
NaH_2PO_4 . 0 H_2O	0. 2-1.2 mg/g
Na_2HPO_4 . 2 H_2O	4.0-5.0 mg/g
Polysorbate	6-7 mg/g
Disodium edetate	1.0-1.5 mg/g
Sodium chloride	5.0-6.0 mg/g
Water for injection	ad 1000 g

Example 5

Alcoholic gel containing primycin as active substance

Composition:

Primycin	0.5 mg/g
Carbomera	10.0 mg/g
Triethanolamine	15.0 mg/g
Polysorbate	15.0 mg/g
Isoadipate	60 mg/g
Ethanol (96%)	500 mg/g
Purified water	300 mg/g

Preparation:

Carbomera is swollen in isoadipate. Primycin is dissolved in the mixture of ethanol and purified water with moderate heating. The solution is stirred till it cools down to room temperature. To this solution Carbomera isoadipate dispersion is added. Then triethanolamine is added and the resultant dispersion is stirred till full gelation.

Example 6

Other alcoholic gel compositions

These alcoholic gels are prepared according to the procedure described in example 5 applying one of the following active ingredients in the following concentration ranges.

Ingredients:

Primycin or Primycin component or Combination of primycin components	0.01 – 10.0 mg/g
Carbomera	7.0-14 mg/g
Triethanolamine	15-20 mg/g
Polysorbate	15-20 mg/g
Isoadipate	50-70 mg/g
Ethanol (96%)	400-600 mg/g
Purified water	300-400 mg/g

Advantages of the invention

Spreading of methicillin- and /or vancomycin-resistant Gram-positive pathogens

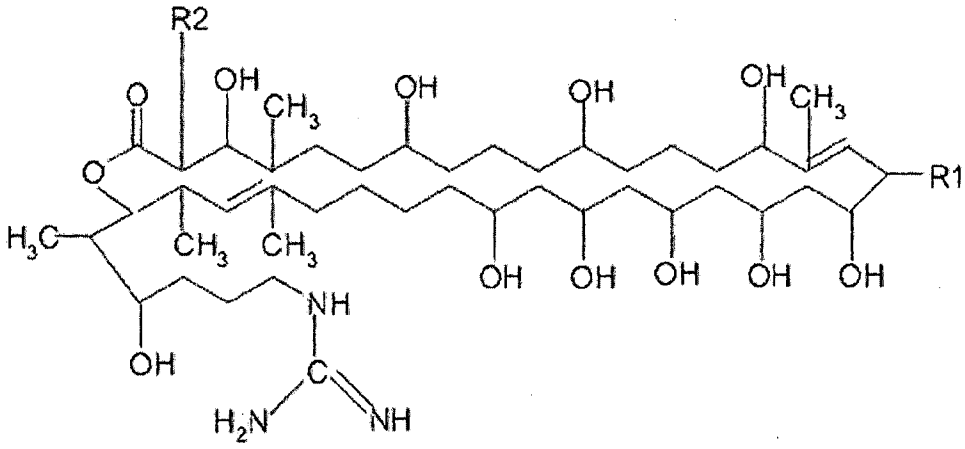
substantially accelerated in the last decades, which rendered all antibiotics affecting these bacteria very valuable both socially and economically.

The present invention is based on newly discovered advantages of a registered active pharmaceutical ingredient with well estabilished use, and thus it offers rapid help in this very urgent need. Primycin and its components are expected to be useful in the treatment of infected people and in the eradication of asymptomatic colonisations from hosts more efficiently than other agents used for this purpose earlier.

Claims

1. Primycin or a primycin component or a combination of primycin components for use in the treatment or prevention of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococcus sp.* (MRCoNS), vancomycin-intermediate or vancomycin-resistant *Staphylococcus aureus* (VISA, VRSA), mupirocin-resistant *Staphylococcus sp.*, vancomycin-resistant *Enterococcus sp.* (VRE) or penicillin-resistant *Streptococcus pneumoniae* strains.

2. Primycin or a primycin component or a combination of primycin components for use according to claim 1 where the primycin component is represented by the following general formula (I)



wherein R1 is n-butyl, n-pentyl or n-hexyl and R2 is arabinosyl, H or OH,

which primycin component is in basic form or in salt form, preferably in the form of sulphate or acetate salt.

3. Primycin or a primycin component or a combination of primycin components for use according to claim 1 or 2 where the combination of primycin components comprises 2, 3, 4, 5, 6, 7, 8 or 9 components selected from the following group:

chinopricin (component A1, where R1 = n-butyl; R2 = arabinosyl)

midopricin (component A2, where R1 = n-pentyl; R2 = arabinosyl)

metipricin (component A3, where R1 = n-hexyl; R2 = arabinosyl)

hydropricin (component B1, where R1 = n-butyl; R2 = H)

hymipricin (component B2, where R1 = n-pentyl; R2 = H)

hymetipricin (component B3, where R1 = n-hexyl; R2 = H)

oxypricin (komponens C1, where R1 = n-butyl; R2 = OH)

oxymipricin (komponens C2, where R1 = n-pentyl; R2 = OH)

oxymetipricin (komponens C3, where R1 = n-hexyl; R2 = OH)

4. Primycin or a primycin component or a combination of primycin components for use according to claim 1 or 3 where the combination of primycin components is selected from the following group: A1 and B1 in a ratio of 1:3 to 3:1, A1 and C1 in a ratio of 1:3 to 3:1, B1 and C1 in a ratio of 1:3 to 3:1 or A1, B1 and C1 in a ratio of 4:3:3 to 7:2:1.

5. Primycin or a primycin component or a combination of primycin components for use according to claim 4 where the combination of primycin components is selected from the following group: A1 and B1 in a ratio of 1:3, 1:1 or 3:1, A1 and C1 in a ratio of 1:3, 1:1 or 3:1, B1 and C1 in a ratio of 1:3, 1:1 or 3:1 or A1, B1 and C1 in a ratio of 4:3:3, 6:2:2 or 7:2:1.

6. Pharmaceutical composition containing as active substance primycin or a primycin component or a combination of primycin components for use according to any of claims 1 to 5, together with at least one carrier or vehicle commonly used in the pharmaceutical industry.

7. The pharmaceutical composition according to claim 6 which contains primycin or a primycin component or a combination of primycin components in a concentration range of 0.01 mg/g to 10 mg/g.

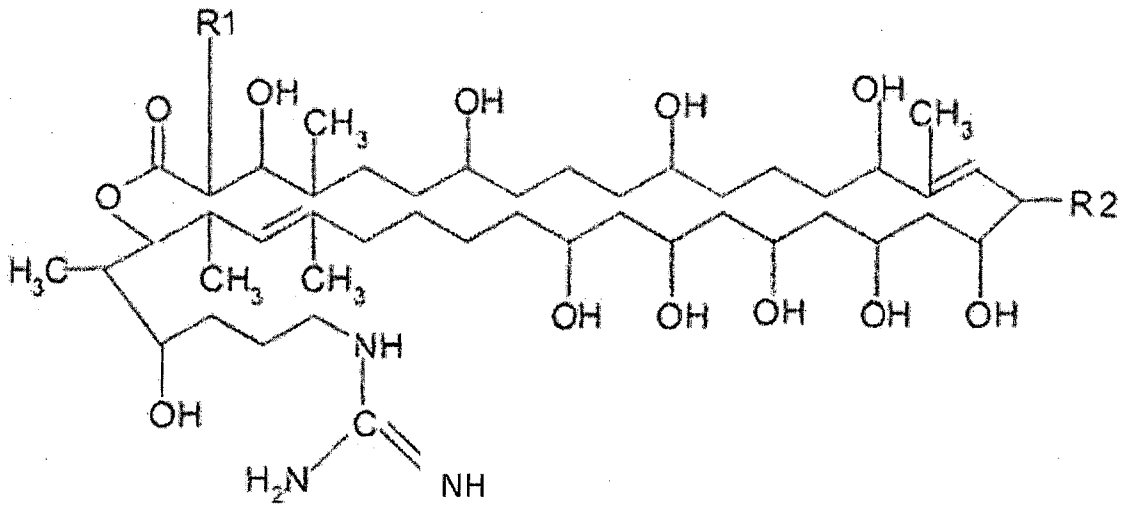
8. The pharmaceutical composition according to claim 7 which contains primycin or a primycin component or a combination of primycin components in a concentration range of 0.1 mg/g to 1.0 mg/g.

9. The pharmaceutical composition according to any of claims 6 to 8 which is applicable on the surface of skin or mucous membrane of a patient or hospital personnel, which pharmaceutical composition is preferably in the form of cream, ointment, gel, solution, suspension, lotion, nasal drops, nasal spray, ear drops or eye drops.

10. The antibacterial composition containing primycin or a primycin component or a combination of primycin components for use according to any of claims 1 to 5, together with at least one carrier or vehicle commonly used in sanitary and hygienic products.

AMENDED CLAIMS
received by the International Bureau on 11 March 2013 (11.03.2013)

1. Primycin or a primycin component represented by the following general formula (I)



wherein R1 is n-butyl, n-pentyl or n-hexyl and R2 is arabinosyl, H or OH,

which primycin component is in basic form or in salt form,

or a combination of said primycin components for use in the treatment or prevention of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococcus sp.* (MRCoNS), vancomycin-intermediate or vancomycin--resistant *Staphylococcus aureus* (VISA, VRSA), mupirocin-resistant *Staphylococcus sp.*, vancomycin-resistant *Enterococcus sp.* (VRE) or penicillin-resistant *Streptococcus pneumoniae* strains.

2. Primycin or a primycin component or a combination of primycin components for use according to claim 1 wherein the primycin componens are in the form of sulphate or acetate salt.

3. Primycin or a primycin component or a combination of primycin components for use according to claim 1 or 2 where the combination of primycin components comprises 2, 3, 4, 5, 6, 7, 8 or 9 components selected from the following group:

chinopricin (component A1, where R1 = n-butyl; R2 = arabinosyl)

midopricin (component A2, where R1 = n-pentyl; R2 = arabinosyl)

metipricin (component A3, where R1 = n-hexyl; R2 = arabinosyl)

hydropricin (component B1, where R1 = n-butyl; R2 = H)

hymipricin (component B2, where R1 = n-pentyl; R2 = H)

hymetipricin (component B3, where R1 = n-hexyl; R2 = H)

oxypricin (component C1, where R1 = n-butyl; R2 = OH)

oxymipricin (component C2, where R1 = n-pentyl; R2 = OH)

oxymetipricin (component C3, where R1 = n-hexyl; R2 = OH).

4. Primycin or a primycin component or a combination of primycin components for use according to claim 1 or 3 where the combination of primycin components is selected from the following group: A1 and B1 in a ratio of 1:3 to 3:1, A1 and C1 in a ratio of 1:3 to 3:1, B1 and C1 in a ratio of 1:3 to 3:1 or A1, B1 and C1 in a ratio of 4:3:3 to 7:2:1.

5. Primycin or a primycin component or a combination of primycin components for use according to claim 4 where the combination of primycin components is selected from the following group: A1 and B1 in a ratio of 1:3, 1:1 or 3:1, A1 and C1 in a ratio of 1:3, 1:1 or 3:1, B1 and C1 in a ratio of 1:3, 1:1 or 3:1 or A1, B1 and C1 in a ratio of 4:3:3, 6:2:2 or 7:2:1.

6. Pharmaceutical composition containing as active substance primycin or a primycin component or a combination of primycin components for use according to any of claims 1 to 5, together with at least one carrier or vehicle commonly used in the pharmaceutical industry.

7. The pharmaceutical composition according to claim 6 which contains primycin or a primycin component or a combination of primycin components in a concentration range of 0.01 mg/g to 10 mg/g.

8. The pharmaceutical composition according to claim 7 which contains primycin or a primycin component or a combination of primycin components in a concentration range of 0.1 mg/g to 1.0 mg/g.

9. The pharmaceutical composition according to any of claims 6 to 8 which is applicable on the surface of skin or mucous membrane of a patient or hospital personnel, which pharmaceutical composition is preferably in the form of cream, ointment, gel, solution, suspension, lotion, nasal drops, nasal spray, ear drops or eye drops.

10. The antibacterial composition containing primycin or a primycin component or a combination of primycin components for use according to any of claims 1 to 5, together with at least one carrier or vehicle commonly used in sanitary and hygienic products.

INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2012/000111

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/7048 A61P31/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VALYI-NAGY T ET AL: "Primycin, a new antibiotic", NATURE: INTERNATIONAL WEEKLY JOURNAL OF SCIENCE, NATURE PUBLISHING GROUP, UNITED KINGDOM, vol. 174, no. 4441, 11 December 1954 (1954-12-11), pages 1105-1106, XP009165902, ISSN: 0028-0836 page 1106, left-hand column, last paragraph ----- -/--	1-10

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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Date of the actual completion of the international search	Date of mailing of the international search report
21 December 2012	08/01/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Collura, Alessandra

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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