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NOTICE OF ENTITLEMENT

We, **GRUPPO LEPETIT S.p.A.** of Via Roberto Lepetit, 8, I-20020 Lainate, Italy state the following in connection with Australian Application No. 16636/95:

1. We are the nominated person.
2. The nominated person is the assignee of the actual inventors.
3. The nominated person is the applicant of the basic application listed in the declaration under Article 8 of the PCT.
4. The basic application is the application first made in a Convention country in respect of the invention.

Dated: 28 June 1996

By **PHILLIPS ORMONDE & FITZPATRICK**  
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To: The Commissioner of Patents

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CENTRAL VENOUS CATHETERS LOADED WITH ANTIBIOTICS OF THE RAMOPLANIN GROUP  
PREVENTING DEVELOPMENT OF CATHETER RELATED INFECTIONS
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- (56) Prior Art Documents  
WO 84/01102  
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- (57) Claim

1. A central venous polyurethane catheter with a thin hydrophilic layer on the surfaces loaded with an antibiotic of the ramoplanin group or any mixture thereof.

9. A process for preparing a central venous polyurethane catheter with a thin hydrophilic layer on the surfaces loaded with an antibiotic of the ramoplanin group or any mixture thereof characterized in that the polyurethane catheter coated with the thin hydrophilic film is incubated in an aqueous solution of the selected antibiotic or any mixture thereof at a concentration varying from 1 to 50 mg/ml, preferably 5 to 30 mg/ml at a temperature between 10°C and 60°C, preferably between 20°C and 40°C for a period varying from 5 minutes to 48 hours, preferably from 10 minutes to 30 hours.

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10. A method for preventing catheter related infection in a patient in need of application of a central venous catheter consisting in the insertion into the patient of a central venous polyurethane catheter coated with a thin hydrophilic layer on the surfaces loaded with an amount of an antibiotic of the ramoplanin group or any mixture thereof sufficient to inhibit the bacterial growth.

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<p>(54) Title: CENTRAL VENOUS CATHETERS LOADED WITH ANTIBIOTICS OF THE RAMOPLANIN GROUP PREVENTING DEVELOPMENT OF CATHETER RELATED INFECTIONS</p>		
<p>(57) Abstract</p> <p>The invention relates to central venous polyurethane catheters with a thin hydrophilic coating loaded with an antibiotic of the ramoplanin group or any mixture thereof and their use in preventing catheter related infections. These catheters are useful to prevent bacterial adherence and colonization and, therefore, to lower the risk of vascular infections in catheterized patients. The method of preparing the catheter of the invention consists in incubating polyurethane catheters coated with a hydrophilic film in an aqueous solution of the selected antibiotic.</p>		

5       **CENTRAL VENOUS CATHETERS LOADED WITH ANTIBIOTICS OF THE  
          RAMOPLANIN GROUP PREVENTING DEVELOPMENT OF CATHETER  
          RELATED INFECTIONS**

10           This invention relates to central venous  
polyurethane catheters with a thin hydrophilic coating  
loaded with an antibiotic of the ramoplanin group, the  
method for their preparation and their use in preventing  
development of catheter related infections in patients.

15           The catheters of this invention are useful to  
prevent bacterial adherence and colonization and,  
therefore, to lower the risk of vascular infections in  
catheterized patients.

          Infections of central venous lines represent a  
20   challenging problem in modern medicine (1-4).  
Contamination of the catheter by skin flora during  
insertion is thought to be one of the major routes in  
the development of catheter infections. Gram-positive  
bacteria like Staphylococcus aureus and coagulase  
25   negative staphylococci (CNS) are the predominant  
causative organisms.

          Catheter infections may lead to severe  
complications for a patient, and, even if they are not  
life-threatening, they may contribute to a prolongation  
30   of hospital stay and to an increase in therapy costs.  
Most of the catheter infections can be managed by  
removing the catheter if clinical signs of infection  
occur; this is normal clinical routine procedure in  
patients having short peripheral venous lines.

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In cases of difficulties for venous access, however, and especially in patients with a long-term central venous catheter, keeping the catheter in place despite the infection is desired. In many cases, however, antibiotic therapy is not able to eliminate bacteria from the catheter.

The failure of antibiotic therapy is mainly due to the existence of a slime barrier (biofilm) which hinders the antibiotic in penetrating and in reaching the adherent bacterial cells.

It was discovered by many investigators that the MIC- or MBC-values of antibiotics for bacteria embedded in a biofilm are much higher than those for bacteria in suspension (5, 6, 7).

An alternative strategy to treat and especially to prevent catheter infections is the coating or loading of medical devices with antimicrobial substances (8-10). The release of the antimicrobial substance (e.g. an antibiotic) from the catheter surface or from the interior leads to a high local drug concentration which should be sufficiently high to reach the MIC and MBC of bacteria in biofilms. Furthermore, local antimicrobial action shortly after catheter insertion would probably inhibit the production of a biofilm by the bacteria. There are already a number of investigations on the coating or loading of catheter materials with antimicrobial substances, mainly with antibiotics (11-15, 16). Such systems show in part good in vitro performances; in a few cases there have already been clinical trials with antimicrobial-coated catheters (11, 17).

Development of resistance to commonly used antibiotics, for instance, due to resistant

Staphylococcus aureus strains (see M.E. Reverdy et al., "Evolution de la résistance aux antibiotiques et aux antiseptiques de souches hospitalières de Staphylococcus aureus isolées de 1980 à 1991" published in Pathologie Biologie, 1993, Vol. 41, No. 9 897-904), is a further factor which makes difficult the management of infections in hospitals and favors any possible employment of antibiotics not yet utilized in the clinical practice.

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According to one aspect of the present invention there is provided a central venous polyurethane catheter with a thin hydrophilic layer on the surfaces loaded with an antibiotic of the ramoplanin group or any mixture thereof, in a concentration sufficient to inhibit the bacterial colonization of the catheter after its insertion into the patient. The catheters of this invention can be maintained in place for the desired period without incurring severe complications for the catheterized patient.

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According to in vitro experiments described by B. Jansen et al. (18), it has been found that teicoplanin has appropriate biological and physico-chemical characteristics to allow absorption on the thin hydrophilic layer coating the surfaces of certain central venous polyurethane catheters. The release of antibacterially active concentrations of the substance in an elution fluid is taken as an effect which may be correlated with the prevention of the bacterial colonization of the catheter and, therefore, the development of an infection in a patient.

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Following the generic indications given by the same authors, the glyco or lipopeptide antibiotics such as vancomycin, daptomycin and ramoplanin would not

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appear to be useful for the preparation of central venous catheters preventing the catheter related infections in view of their poor absorption/release properties.

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According to this invention, it has been surprisingly discovered that the central venous polyurethane catheters with a thin hydrophilic layer on the surfaces loaded with an antibiotic of the ramoplanin group or any mixture thereof, are effective in  
10 inhibiting development of bacterial colonization and preventing catheter related infections after the insertion into the patients.

15 Therefore, a further aspect of this invention is a method of preventing <sup>or reducing</sup> catheter related infections in a patient in need of application of a central venous catheter, such method consisting in the insertion into  
20 the patient of a central venous polyurethane catheter with a thin hydrophilic layer on the surfaces loaded with an antibiotic of the ramoplanin group or any mixture thereof.

25 Ramoplanin is an International Non-Proprietary Name which identifies the antibiotic complex originally designated as A/16686.

Antibiotic A/16686 is an antibiotic produced by Actinoplanes sp. ATCC 33076 active against aerobic and  
30 anaerobic gram-positive bacteria, including methicillin-resistant Staphylococci and bacteria resistant to ampicillin and erythromycin and it is described in U.S. Patent 4,303,646 together with its manufacture process and pharmaceutical composition  
35 containing it.

Preliminary physico-chemical characterization indicated by Cavalleri et al. (19) that antibiotic A/16686 is formed by a peptidic core carrying two D-mannose units.

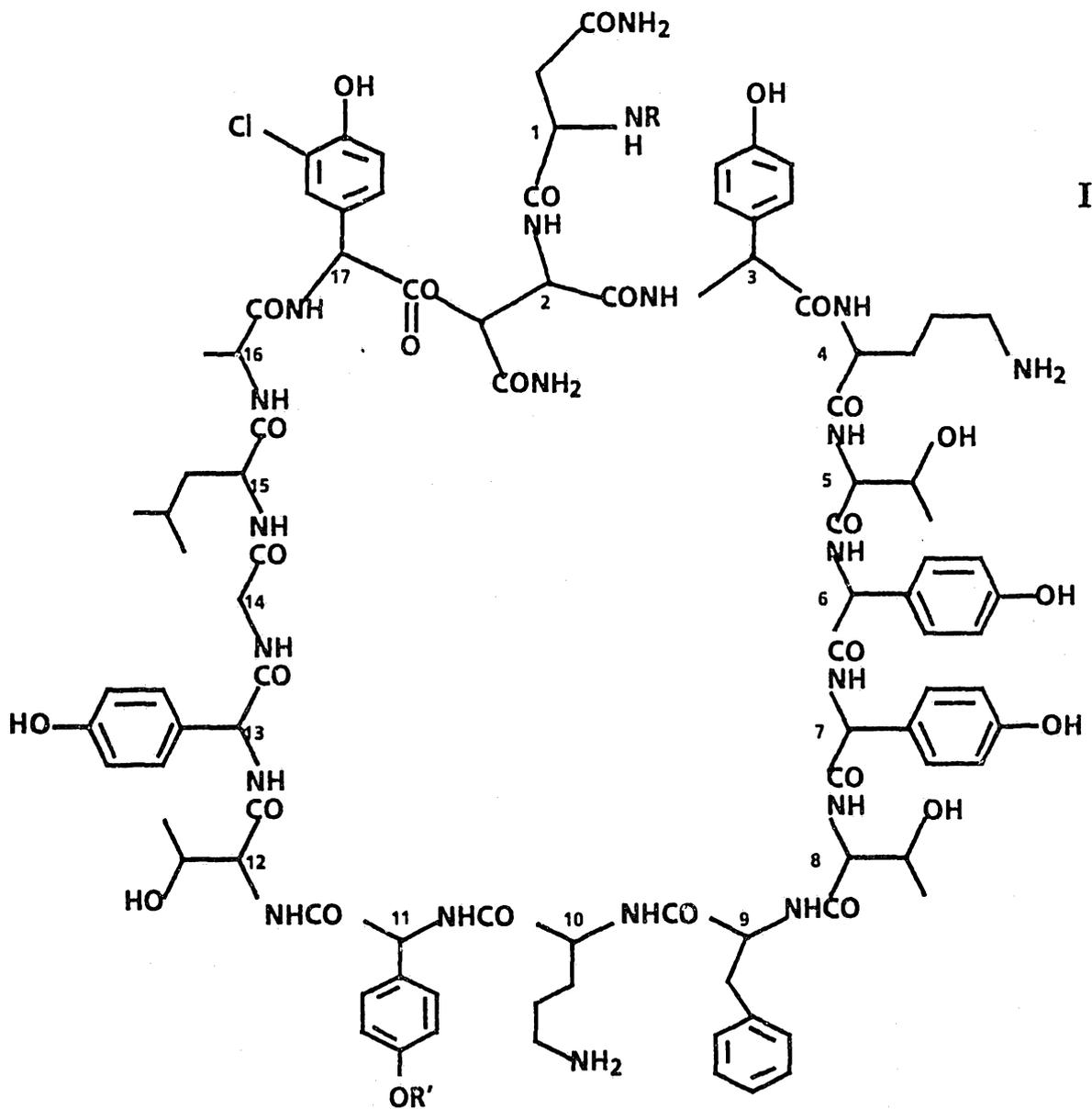
It was then found that three closely related major components could be isolated from antibiotic A/16686 which were named factor A1, A2 and A3. Factor A2 is the component obtained in preponderant amount and is the most relevant for the biological activity, while factor A1 and A3 are obtained in a minor amount. These substances as well as their preparation and uses are described in U.S. Patent 4,427,656.

It is however possible to modulate the proportion of the three above major components in the complex obtained by fermentation of the microorganism Actinoplanes sp. ATCC 33076. In fact, a method for selectively enhancing the production of factors A2 and/or A3 of antibiotic A/16686 by adding appropriate precursors to an A/16686 producing culture, is described in European Patent Application Publication No. 259780.

Recent studies showed that these three factors have a common cyclic depsipeptide skeleton composed by seventeen aminoacids and a dimannosyl unit. Three different unsaturated fatty acid residues differentiate the three components of the complex.

The antibiotics characterized by the simultaneous presence of a depsipeptide skeleton, fatty acids and sugar moieties have been defined in the scientific literature as glycolipodepsipeptide antibiotics (20).

The following formula I can be suggested for the three closely related components of antibiotic A/16686:



wherein:

R is:  $-\text{CO}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_3$ ,  
 $-\text{CO}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$  or  
 $-\text{CO}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)_2$  and

R' is a dimannosyl moiety.

European Patent Application Publication No. 318680 describes other compounds related to antibiotic A/16686 complex.

Said compounds, named factors A'1, A'2 and A'3  
5 respectively, are produced by Actinoplanes sp. ATCC 33076 under appropriate conditions and correspond to factors A1, A2 and A3 of formula I wherein R' is a mannosyl moiety.

10 Catalytic hydrogenation of each of the factors A and/or A' or their mixtures, yields the corresponding derivatives tetrahydrogenated in the fatty acid chain portions. European Patent Application Publication No. 321696 describes the tetrahydrogenated derivatives of  
15 the several factors A and A' of A/16686 complex and mixtures thereof and their method of manufacture.

European Patent Application Publication No. 337203 describes the obtainment of the aglycons of the  
20 components of the A/16686 antibiotic complex and their derivatives hydrogenated in the fatty acid chain portions. The cleavage of the glycosyl moiety is achieved by selective hydrolysis.

25 In this description and claims the term "antibiotic of the ramoplanin group" identifies any single factor of the A/16686 complex and any derivative thereof among those described above.

The expression "any mixture thereof" in this  
30 description and claims identifies any mixture of two or more compounds selected from the factors of the A/16686 complex and the derivatives thereof mentioned above, in any proportion.

When used alone and not otherwise specified, the  
35 term "ramoplanin" usually identifies the factor A2 of

A/16686 or a preparation containing at least 80% (with respect to the whole antibiotic substance, by HPLC assay) of such factor A2, the remaining portion consisting essentially of small amounts of the related A  
5 and A' factors. Preparations of this type are currently obtained from pilot or semi-industrial fermentation and recovery operations.

10 Central venous polyurethane catheters with a thin hydrophilic coating on the surfaces which can be advantageously utilized according to this invention are described in the literature. For instance, US 4769013  
15 catheters, with a poly-N-vinylpyrrolidone-polyurethane interpolymer useful to form coated devices which can release antibacterial agents adsorbed thereon.

20 US 4950256 reports a series of references to methods of coating medical devices, including catheters, with a thin hydrophilic layer with low friction in wet conditions and improved blood compatibility and describes an intravascular catheter coated with  
25 hydrophilic polymer having adsorbed an amount of the cationic cyclic polypeptide antibiotic polymixin sufficient to inhibit the growth of bacteria and the formation of blood clots. Polymixin is an antibiotic generally active against gram-negative bacteria.

30 Catheters which have been found particularly suitable for use in the embodiment of this invention are polyurethane catheters with a thin hydrophilic coating on both the internal and external surface based on a poly-N-vinylpyrrolidone-polyurethane interpolymer of  
35 approximately 200  $\mu\text{m}$  thickness, marketed under the trade

name Hydrocath® (Viggo-Spectramed, Swindon, Wiltshire, England).

These hydrophilic central venous catheters (which are available as single, double and triple lumen types),  
5 due to their coating, show a percent swelling after incubation at room temperature for 24 hours in water, water:ethanol 1:1 or ethanol of, respectively, 8.0, 16.1 and 30.5.

According to the method of preparing the catheter  
10 of this invention, the above mentioned polyurethane catheters coated with a hydrophilic film are incubated in an aqueous solution of an antibiotic of the ramoplanin group or any mixture thereof, preferably, ramoplanin, at a concentration varying from 1 to 50  
15 mg/ml, preferably 5 to 30 mg/ml at a temperature between 10°C to 60°C, preferably between 20°C and 40°C for a period varying from 5 minutes to 48 hours, preferably from 10 minutes to 30 hours.

20 During the above incubation period, relatively large amounts of antibiotic of the ramoplanin group or any mixture thereof can bind to the catheter.

Since the above parameters are generally  
25 correlated, their influence on the loading of the catheters may be evaluated by carrying out a series of loading experiments wherein the concentration of the solution of the antibiotic of the ramoplanin group or any mixture thereof, the incubation temperature and the  
30 time are varied.

An indication of the amount of the antibiotic of the ramoplanin group or any mixture thereof loaded on the catheter according to the method of this invention,  
35 may be obtained by means of incubation of the loaded

catheter (after washing with demineralized water and drying overnight under vacuum) at room temperature in a 8M guanidine hydrochloride water solution, for a planned time. The amount of antibiotic eluted in the guanidine  
5 solution is then evaluated by microbiological assay. The appropriate incubation time is determined by verifying whether a second incubation period in a fresh 8M guanidine hydrochloride solution, followed by microbiological assay, shows further release of  
10 antibiotic or not. Current experiments of incubation in a 8M guanidine hydrochloride water solution have demonstrated that after the incubation period of one hour no further release of antibiotic from the loaded catheter into the fresh guanidine hydrochloride solution  
15 is observed.

When the above loading conditions are applied, the amount of antibiotic released in the 8M guanidine hydrochloride solution of incubation, when related to  
20 the catheter length, generally corresponds to a value ranging from 20  $\mu\text{g}/\text{cm}$  to 100  $\mu\text{g}/\text{cm}$ .

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The efficacy of the central venous catheter loaded with an antibiotic of the ramoplanin group or any mixture thereof in preventing catheter related infections, was demonstrated in animal experiments. The method utilized for the above mentioned experiments is described by G. Romanò et al. (21).

Segments (1 cm) of Hydrocath® catheter (coated or uncoated with the antibiotic) were inserted subcutaneously in anesthetized mice (male and female CD-1 mice, Charles-River) 96 h, 48 h and immediately before infection. 0.1 ml of a bacterial suspension of Staphylococcus aureus L 1162 was injected subcutaneously in close proximity to the catheter segments. Bacterial suspensions consisted of approximately  $2 \times 10^8$  CFU/ml for S. aureus L 1162 prepared in BBL Trypticase soy broth from overnight growth on 7% sheep blood agar plates. Twenty-four and 48 hours after infection, catheters were removed and placed individually into 5 ml of PBS.

Bacteria were then harvested from catheters. Each catheter was washed three times in 5 ml of PBS and finally covered with 2 ml of PBS in a glass tube. Bacteria adhering to the catheter were removed by sonication at 90-100  $\mu$ A of two cycles of 45 seconds each with an intervening period of 3 seconds. This treatment was shown in preliminary experiments to remove all adherent bacteria, since no growth was observed around catheters placed on Difco Todd-Hewitt agar plates after sonication and it had no detrimental effects on bacterial viability. Bacteria dislodged from the catheter were subsequently diluted in PBS and 0.1 ml aliquots of suitable dilutions spread onto Difco Todd-Hewitt agar plates to determine the number of viable bacteria.

Table I and Table II report the results of the experiments on the in vivo efficacy of catheters loaded with ramoplanin in preventing colonization with S. aureus L 1162 compared with that of catheters loaded  
5 with teicoplanin.

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**TABLE I**  
***S. aureus* L 1162 adherence on Hydrocath® catheters inserted in the mouse 48 and 0 hours before infection**

Group	Infection (h after catheter insertion)	Extraction (h after catheter infection)	Mean Log <sub>10</sub> CFU/cat (SD)
Control	0	24	4.4 (1.8)
		48	5.3 (0.9)
	48	24	4.3 (1.2)
		48	5.5 (0.6)
Ramoplanin	0	24	≤1.0 (0)
		48	≤1.0 (0)
	48	24	1.9 (0.8)
		48	1.8 (1.1)
Teicoplanin	0	24	1.3 (0.4)
		48	1.7 (0.8)
	48	24	2.0 (1.3)
		48	1.6 (0.9)

**TABLE II**  
***S. aureus* L 1162 adherence on Hydrocath® catheters inserted in the mouse 96 and 0 hours before infection**

Group	Infection (h after catheter insertion)	Extraction (h after catheter infection)	Mean Log <sub>10</sub> CFU/cat (SD)
Control	0	24	5.1 (0.5)
		48	5.2 (1.2)
	96	24	4.7 (1.1)
		48	4.6 (1.1)
Ramoplanin	0	24	≤1.0 (0)
		48	≤1.0 (0)
	96	24	2.3 (1.1)
		48	1.8 (0.8)
Teicoplanin	0	24	2.2 (1.2)
		48	1.6 (1.4)
	96	24	2.8 (0.9)
		48	2.0 (1.0)

The results of the above experiments indicate that ramoplanin coating of catheters can prevent colonization of the catheter by S. aureus for a period of at least 144 hours after the insertion into the patient and at least 48 hours after bacterial contamination. Of particular interest was the finding that ramoplanin coating was generally more effective than teicoplanin coating, especially, when the catheter insertion was made immediately before infection.

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Additional examination of the uninfected animals bearing catheters loaded with ramoplanin revealed no evidence of local inflammation confirming the good tolerability of the ramoplanin loaded central venous catheters.

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## CLAIMS

- 5                   1. A central venous polyurethane catheter  
with a thin hydrophilic layer on the surfaces loaded  
with an antibiotic of the ramoplanin group or any  
mixture thereof.
- 10                   2. A central venous catheter of claim 1  
further characterized in that the catheter is loaded  
with an amount of antibiotic of the ramoplanin group or  
any mixture thereof, in concentration sufficient to  
inhibit the bacterial colonization of the catheter,  
15 after insertion into the patient.
3. A catheter of any of claims 1 and 2  
                  *wherein* it is loaded with an antibiotic of  
the ramoplanin group selected from the group consisting  
20 of: antibiotic A/16686 factor A2, antibiotic A/16686  
factor A1, antibiotic A/16686 factor A3, antibiotic  
A/16686 factor A'1, antibiotic A/16686 factor A'2,  
antibiotic A/16686 factor A'3, any of the derivatives  
thereof hydrogenated in the fatty acid chain, any of the  
25 aglycons thereof, and any mixture thereof.
4. A catheter of any of claims 1 to 3  
wherein the thin hydrophilic layer consists essentially  
of a poly-N-vinylpyrrolidone polyurethane interpolymers.  
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5. A catheter of claims 1 to 4 wherein the  
hydrophilic layer has a thickness of approximately  
200  $\mu\text{m}$ .

6. A catheter as in any of claims 1 to 5 wherein the antibiotic loaded is ramoplanin.

7. A catheter of claim 6 wherein,  
5 when incubated for one hour at room temperature in a 8M guanidine hydrochloride solution, it releases into the solution an amount of antibiotic that, when related to the catheter length, corresponds to a value ranging from 20  $\mu\text{g}/\text{cm}$  to 100  $\mu\text{g}/\text{cm}$ .

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8. A catheter of any of claims 1 to 7 for use in preventing catheter related infection in patients needing application of central venous catheters.

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9. A process for preparing a central venous polyurethane catheter with a thin hydrophilic layer on the surfaces loaded with an antibiotic of the ramoplanin group or any mixture thereof characterized in that the polyurethane catheter coated with the thin  
20 hydrophilic film is incubated in an aqueous solution of the selected antibiotic or any mixture thereof at a concentration varying from 1 to 50 mg/ml, preferably 5 to 30 mg/ml at a temperature between 10°C and 60°C, preferably between 20°C and 40°C for a period varying  
25 from 5 minutes to 48 hours, preferably from 10 minutes to 30 hours.

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~~10. Use of an antibiotic of the ramoplanin group or any mixture thereof for preparing a central venous catheter for preventing development of bacterial infections related with insertion of central venous catheters into patients.~~

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~~11. Use according to claim 10 wherein the antibiotic of the ramoplanin group or any mixture~~

10. A method for preventing catheter related infection in a patient in need of application of a central venous catheter consisting in the insertion into the patient of a central venous polyurethane catheter coated with a thin hydrophilic layer on the surfaces loaded with an amount of an antibiotic of the  
5 ramoplanin group or any mixture thereof sufficient to inhibit the bacterial growth.

11. A method as in claim 10 wherein the antibiotic of the ramoplanin group or any mixture thereof is selected from: antibiotic A/16686 factor A2, antibiotic A/16686 factor A1, antibiotic A/16686 factor A3, antibiotic A/16686  
10 factor A'1, antibiotic A/16686 factor A'2, antibiotic A/16686 factor A'3, any of the derivatives thereof hydrogenated in the fatty acid chain, any of the aglycons thereof, and any mixture thereof.

12. A method as in claim 10 wherein the antibiotic is ramoplanin.  
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13. A method according to claim 1 substantially as hereinbefore described with reference to the tabulated experimental results.  
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INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 95/00355

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61L29/00</p>		
<p>According to International Patent Classification (IPC) or to both national classification and IPC</p>		
<p>B. FIELDS SEARCHED</p>		
<p>Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61L</p>		
<p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p>		
<p>Electronic data base consulted during the international search (name of data base and, where practical, search terms used)</p>		
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO-A-92 15286 (NOVA PHARMACEUTICAL CORP.) 17 September 1992 see page 9, line 22 - line 28 see page 10 - page 11; claims ---	1
X	EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY & INFECTIOUS DISEASES, vol. 12, no. 7, July 1993 pages 545-548, A. KROPEC ET AL. 'IN VITRO ACTIVITY OF VANCOMYCIN AND TEICOPLANIN AGAINST STAPHYLOCOCCUS AUREUS AND STAPHYLOCOCCUS EPIDERMIS COLONIZING CATHETERS' see the whole document --- -/--	1
<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.      <input checked="" type="checkbox"/> Patent family members are listed in annex.</p>		
<p>* Special categories of cited documents :</p> <p>'A' document defining the general state of the art which is not considered to be of particular relevance</p> <p>'E' earlier document but published on or after the international filing date</p> <p>'L' document which may throw doubt, on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>'O' document referring to an oral disclosure, use, exhibition or other means</p> <p>'P' document published prior to the international filing date but later than the priority date claimed</p> <p>'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>'&amp;' document member of the same patent family</p>		
<p>Date of the actual completion of the international search  29 May 1995</p>		<p>Date of mailing of the international search report  09.06.95</p>
<p>Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016</p>		<p>Authorized officer  ESPINOSA, M</p>

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 95/00355

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>THE JOURNAL OF HOSPITAL INFECTION, vol. 24, 1993 pages 211-218, A. PASCUAL ET AL. 'EFFECT OF POLYURETHANE CATHETERS AND BACTERIAL BIOFILMS ON THE IN-VITRO ACTIVITY OF ANTIMICROBIALS AGAINST STAPHYLOCOCCUS EPIDERMIS' see abstract</p> <p style="text-align: center;">---</p>	1
X	<p>ZENTRALBLATT FÜR BAKTERIOLOGIE, vol. 279, no. 3, August 1993 pages 426-433, G. ROMANO ET AL. 'EFFICACY OF A CENTRAL VENOUS CATHETER (HYDROCATH R) LOADED WITH TEICOPLANIN IN PREVENTING SUBCUTANEOUS STAPHYLOCOCCAL INFECTION IN THE MOUSE' cited in the application see page 431</p> <p style="text-align: center;">---</p>	1
X	<p>THE JOURNAL OF HOSPITAL INFECTION, vol. 22, no. 2, October 1992 pages 93-107, B. JANSEN ET AL. 'IN-VITRO EFFICACY OF A CENTRAL VENOUS CATHETER ("HYDROCATH") LOADED WITH TEICOPLANIN TO PREVENT BACTERIAL COLONIZATION' cited in the application see the whole document</p> <p style="text-align: center;">---</p>	1
P,X	<p>EP-A-0 590 348 (GRUPPO LEPETIT S.P.A.) 6 April 1994 see the whole document</p> <p style="text-align: center;">---</p>	1-15
A	<p>EP-A-0 328 421 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 16 August 1989 see claims</p> <p style="text-align: center;">---</p>	1,4
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A	<p>WO-A-84 01102 (HYDROMER, INC.) 29 March 1984 cited in the application see claims; examples 1-5 &amp; US-A-4 769 013</p> <p style="text-align: center;">-----</p>	1

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Information on patent family members

Int. Patent Application No

PCT/EP 95/00355

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