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— *of inventorship (Rule 4.17(iv)) for US only*

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

(54) **Title:** ORAL ANTIMICROBIAL PHARMCEUTICAL COMPOSITIONS

(57) **Abstract:** The present invention relates to oral pharmaceutical compositions with controlled and/or programmed release containing at least one active ingredient having antimicrobial and/or anti-infectious activity for the treatment of infections of the large intestine, in particular the colon.

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Title

Oral antimicrobial pharmaceutical compositions

Description

Intestinal infections are common diseases caused by the colonization of the intestine by foreign pathogenic agents of various origins, or caused by intestinal microorganisms that are normally present becoming virulent.

It is known that the intestine is divided into two distinct portions: the proximal portion, called the "small intestine", which is formed, in the craniocaudal direction, by the duodenum, the jejunum and the ileum, and the distal portion, called the "large intestine", which is formed by the colon and the recto-anus *(Faller A, Scevola G. Anatomia e Fisiologia del Corpo Umano (Anatomy and Physiology of the Human Body). Vol I. Edizioni Minerva Medica, Turin, 1973, pp. 235-254).*

The two portions, the small intestine and the large intestine, are completely separated anatomically by the ileocaecal valve which permits the passage of the intestinal contents from the small intestine to the large intestine but not vice versa.

Besides from the anatomical-structural point of view, the large intestine is quite different from the small intestine also, and above all, from the functional point of view *(Braga PC. Enteric microflora and its regulation. In Drugs in Gastroenterology. Raven Press, New York, 1991, pp. 501-508).*

While the small intestine is assigned to the digestion of the majority of the food, to the absorption thereof, to the production of B-complex vitamins and vitamin K, to the metabolism of biliary acids and various other organic substances and to the rapid transfer of the alimentary bolus to the sections further downstream, the large intestine provides for the absorption of water, for the digestion of vegetable fibres and for the completion of some digestive processes initiated in the small intestine.

In addition, the large intestine differs from the small intestine by the presence of an extremely rich bacterial flora, the balance of which is of fundamental importance in regulating the ambient pH, motility, the production of gas and ammonia, the formation of faeces, and the production of metabolites essential for maintaining the good functioning of the large intestine.

These many differences between the small intestine and the large intestine explain

the distinctive nature of some pathologies which occur at the expense of the large intestine and in particular the colon.

The colon is the portion of the large intestine that is host to the majority of the bacterial strains and that offers conditions of pH, anaerobiosis, humidity and slowness of transit that are particularly suitable for the permanent flora potentially becoming virulent or for the proliferation of and colonization by pathogenic bacteria. For those reasons, the colon is the sector of the intestine most susceptible to infection; in fact, infections located in the colon (infectious colites, bacillary dysentery, diarrhoea, pseudomembranous colitis, diverticulitis, etc.) constitute an important and autonomous chapter in the gastroenterological monograph *(Sorice F., Vullo* V. *Intossicazioni alimentari e infezioni del tubo digerente. (Food Poisoning and Infections of the Alimentary Canal). In: Medicina Clinica (Clinical Medicine).Edizioni Medico Scientifiche, Turin, 2002).*

In addition, the increased endoluminal pressure, linked with the production of gas and associated with predisposing local factors, can promote the occurrence of diverticula which are susceptible to infection and inflammation and which are located exclusively in the colon *(Jackson BT. Diverticular disease. In: Inflammatory Bowel Diseases Churchill Livingston, New York, 1997, pp. 443-447).*

Currently, the oral therapy of intestinal infections, and in particular colon infections, uses substances having antibacterial activity which must have specific characteristics such as: broad spectrum of activity on Gram+ and Gram- bacteria, resistance to strongly acidic environments, such as the gastric environment, anti-infectious activity independent of the presence of the intestinal biomass, residence inside the intestine for an appropriate period of time, good penetrability into the infecting host cell and good tolerability *(Braga PC. Interaction of antibiotics on enteric microflora. In: Drugs in Gastroenterology. Raven Press, New York, 1991, pp. 509-517).*

Therapy with antibacterial agents administered in the oral preparations employed today has at least two limitations. In the first place, the antibacterial agents, if not suitably protected, may lose their efficacy owing to the enzymatic or degradative inactivation which occurs during their passage through the stomach or through the

small intestine.

In addition, the pharmaceutical forms nowadays used, although they permit the administration of the active ingredient in discrete doses, release it too rapidly in relation to the time taken to pass through the digestive tract, so that the active ingredient performs its anti-infectious activity in an indiscriminate manner along the entire gastro-intestinal tract.

This leads to the disappearance of the non-pathogenic bacterial flora living in the small intestine (duodenum, jejunum and the ileum), which flora, since it is not normally the seat of infection, should be protected and not subjected to the sterilizing action characteristic of the formulations used today.

For it is known that this bacterial flora is important in fundamental biological processes, such as, for example, the digestion and absorption of alimentary nutritive components, the production and absorption of vitamins (vitamin K and B-complex vitamins), the metabolism of biliary acids and of steroid hormones, the activation and inactivation of various substances, the protection of the organism from xenobiotics, (*Braga PC. Ibidem).*

In particular, the usual oral antibacterial therapies for the treatment of pathologies located in the colon have often given a contradictory result, probably owing to the excessive dilution of the active ingredients in the intestinal lumen; this dilution is caused by the premature release of the antimicrobial agent from the pharmaceutical form containing it, which takes place as early as in the stomach and in the immediate vicinity of the patient's pyloric valve.

In addition, although the antimicrobial agents used for the disinfection of the digestive tract often do not have a high rate of metabolism, in order to maintain unaltered the therapeutic possibility connected with the administration of a traditional form containing antimicrobial agents, no phenomenon of metabolic degradation should occur, in order to avoid any weakening of the therapeutic efficacy associated with the presence of the antimicrobial agent.

Therefore, in such cases, in order to ensure the real efficacy of the anti-infectious therapy, it is felt that there is a need for the possibility of a controlled and site-specific form of administration.

For the release of the antimicrobial/anti-infectious active ingredient in the

immediate vicinity of the region where a diverticulum or a generic infection becomes established, leads to the formation of a much higher concentration gradient than in the case of a conventional form of oral administration, with the consequent greater possibility that the antimicrobial agent will succeed in penetrating to the inside of the diverticulum.

In that situation, particular importance is attached to the possibility of the remission also of infectious pathologies which are not widespread but which are of considerable socio-epidemiological importance, such as bacillary dysentery and pseudomembranous colitis, and also of infectious complications in surgical operations at the expense of the large intestine and in particular the colon.

Rifamicin SV, which has been known since the 1960s, is a semi-synthetic active ingredient which is derived from rifamicin S and which has a strong antimicrobial and/or anti-infectious activity both locally and parenterally. Its activity has also been evaluated in vitro at minimum concentrations (mcg/ml) on Gram+ bacteria, such as *Staphylococcus aureus* or *Enterococcus faecalis*, as well as at higher concentrations on Gram- bacteria, such as *Escherichia coli*, *Salmonella, Enterobacter aerogenes, Enterobacter cloacae or Pseudomonas aeruginosa.*

Rifamicin SV, in the form of its sodium salt, is currently marketed under the name Rifocin® both for external topical use and for injection. In particular, the topical use, indicated for the local treatment of infectious processes, is limited to external use by means of a solution of the active ingredient which is to be diluted at the time of use.

Patent application WO01/11077, which is incorporated herein by reference, describes the use of antimicrobial agents, including the generic rifamicin, for the preparation of pharmaceutical compositions that can be used in the treatment of pathologies caused by anomalous bacterial growth (Small Intestine Overgrowth – SIBO) at the expense of the small intestine. Those compositions are formulated in such a manner as to release the active ingredient rapidly in the proximal portion of the intestine, that is to say, solely in the small intestine (duodenum, jejunum and ileum).

Metronidazole is a nitroimidazole chemotherapeutic agent having powerful antimicrobial activity and a broad spectrum of action both on Gram+ bacteria and

Gram- bacteria. In addition, metronidazole is known to have a proven antiprotozoan activity (*Tracy J.W. et al., Metronidazole, in: Goodmen & Gilman's, The Pharmacological Bases of Therapeutics, IX Ed., 1996, pp 995-998*). Current therapy with metronidazole is supported with tablets (Flagyl®) that contain 250 mg of active ingredient and that are formulated for immediate release.

It has now surprisingly been found that the efficacy of antimicrobial/anti-infectious active ingredients, such as rifamicin SV and/or metronidazole, in the treatment of infections of the large intestine, and in particular of the colon, can be substantially potentiated thanks to the elimination of the undesired effects described above (avitaminosis, destruction of non-pathogenic bacterial flora, etc.) which are caused by the premature release of the active ingredients in the first portions of the digestive canal, such as the stomach, the duodenum and the jejunum, and thanks to the protection from the metabolic-enzymatic inactivation of the active ingredients which is brought about before the ingredients can reach the site of infection.

In particular, the efficacy of rifamicin SV was verified by means of an evaluation of the MIC (Minimum Inhibiting Concentration) on specific pathogenic bacterial strains, such as, for example, *Escherichia coli, Enterobacter faecalis, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhi and Enterobacter cloacae* as shown in the following Table A.

TABLE A

Bacterial species	MIC (mcg/ml)
Escherichia coli (ATCC 30218)	400
Enterobacter faecalis (ATCC 29212)	25
Proteus vulgaris (ATCC 13315)	400
Pseudomonas aeruginosa (ATCC 27853)	> 400
Salmonella typhi (ATCC 13331)	> 400
Enterobacter cloacae (ATCC 17446431)	> 400
Staphylococcus aureus (ATCC 25213)	< 0.4

The present invention therefore relates to oral pharmaceutical compositions

containing an active ingredient having antimicrobial/anti-infectious activity, such as rifamicin SV and/or metronidazole, characterized in that they are formulated in such a manner as to release the active substances substantially in the portion of the large intestine where their specific sterilizing action is required, but leaving unaltered the non-pathogenic bacterial flora present in the portions of the small intestine which are not affected by the infection.

In particular, the formulations according to the present invention are capable of releasing the active ingredient solely in the colon, thus ensuring localized and restricted anti-infectious efficacy.

Consequently, the advantage of the formulations of the invention is the particular site-specificity in the large intestine, and in particular in the colon, which permits a greater concentration of the active substance in the infected distal intestinal region with complete preservation of the healthy proximal regions.

This advantage is displayed mainly during the treatment of specific pathological situations in the colon region, such as infectious colites, bacillary dysentery, diverticular disease and diverticulitis where the site-specificity and the tolerability of the formulations play a key role in the resolution of the pathology.

A further advantageous application of the formulations of the invention is their use during preparation for surgical operations on the large intestine, in ileocolic anastomoses, and in the sterilization of the ammonia-producing colonic flora in order to prevent and/or treat hyperammonaemias. In these last-mentioned cases, the site-specificity of treatment and the consequent concentration of the activity of the active ingredient may lead to a significant resolution of cases which would otherwise involve substantial complications.

In the formulations of the invention, the substances having antimicrobial/anti-infectious activity are contained in an amount of from 10 to 90% by weight; in particular rifamicin SV is contained in an amount of from 20 % to 60% by weight, while metronidazole is contained in an amount of from 25% to 70% by weight.

The oral formulations of the invention are selected from tablets, capsules, granules and/or microgranules.

A preferred embodiment of the present invention comprises a system for controlled release which is characterized by the presence of a first, amphiphilic,

matrix in which the active ingredient is incorporated and which is in turn dispersed in a second, lipophilic, matrix. The form so obtained is again in turn dispersed in a third, hydrophilic, matrix before producing the final oral pharmaceutical form.

The lipophilic matrix of the present invention is represented by substances having a melting point lower than 90°C, such as, for example, beeswax, carnauba wax, stearic acid, stearin and the like; the amphiphilic matrix is represented by substances selected, for example, from phospholipids, ceramides, sphingomyelins, lecithins, alkyl block copolymers, salts of sulphated alkyl acids, polyoxyethylenated alkyl, derivatives of sorbitan and the like, while the hydrophilic matrix is represented by generally cross-linked or linear polymeric or copolymeric substances, which are known as hydrogels, that is to say, substances capable of increasing their mass and their weight, owing to the polar groups present in the main or side polymer chains, when they come into contact with molecules of water.

In particular, the hydrophilic matrix corresponds to substances selected, for example, from cellulose derivatives, such as hydroxyalkylcelluloses, alkylcelluloses, carboxyalkylcelluloses and their salts or derivatives, polyvinyl alcohols, carboxyvinyl derivatives, polysaccharide derivatives of anionic or cationic nature, such as, for example, hyduronic acid, glucuronic acid, or glucosamines, pectins and/or their derivatives.

In this preferred embodiment, the matrices are dispersed in one another in succession together with the active ingredient, thus bringing about the formation of a homogeneous structure responsible for the site-specificity of release.

In a further embodiment of the present invention, the tablets obtained are finally subjected to a coating process using gastroresistant substances, such as, for example, polymers of acrylic and methacrylic acids (Eudragit) and/or derivatives of cellulose phthalate.

Systems of controlled and/or programmed release suitable for the present invention are described in EP 1183014, GB 2245492 and EP572942, which are also incorporated herein by reference.

The following Examples describe the invention in detail without limiting the

content thereof in any way.

EXAMPLE 1

200 g of rifamicin SV are mixed with 5 g of stearic acid, 7 g of carnauba wax, 8 g of sodium dioctyl sulphosuccinate, 100 g of lactose and 10 g of sodium edetate and granulated with a solution containing 25 g of low-viscosity polyvinylpyrrolidone in 0.2 litre of purified water. When the granulate has been dried, it is mixed with 100 g of sodium carboxymethylcellulose, 25 g of silica, 5 g of glycerol palmitostearate and 10 mg of talcum before being subjected to compression to the unit weight of 495 mg/tablet. The cores so obtained are then film-coated with a hydroalcoholic dispersion of acrylic and methacrylic acid esters, titanium dioxide, talcum and triethyl citrate, which confers on the product resistance to disintegration in a strongly acidic environment, simulating the environment of the stomach and the small intestine. The dissolution of the tablets is practically zero in pH conditions of less than 7 and is progressive in an enteric buffer at pH 7.2 with the following percentage quotas:

less than 20% after 1 hour's residence,

less than 50% after 3 hours' residence,

more than 70% after 8 hours' residence.

EXAMPLE 2

500 g of rifamicin SV are mixed with 10 g of stearic acid, 10 g of beeswax, 10 g of sodium lauryl sulphate, 200 g of mannitol and 10 g of sodium edetate and granulated with a solution containing 50 g of hydroxypropylcellulose in 0.5 litre of water. When the granulate has been dried, it is mixed with 150 g of sodium hydroxypropylmethylcellulose, 25 g of silica, 5 g of glycerol palmitostearate and 10 mg of talcum before being subjected to compression to the unit weight of 490 mg/tablet. The cores so obtained are then film-coated with an aqueous dispersion of acrylic and methacrylic acid esters, iron oxide, talcum and triethyl citrate, with confers on the product resistance to disintegration in an acidic environment, simulating the environment of the stomach and the small intestine. The dissolution of the tablets is practically zero in pH conditions of less than 7 and is progressive in an enteric buffer at pH 7.2 with the following percentage quotas:

- less than 30% after 1 hour's residence,

- less than 60% after 3 hours' residence,
- more than 80% after 8 hours' residence.

EXAMPLE 3

2.5 kg of metronidazole are mixed with 70 g of stearic acid, 70 g of beeswax, 400 g of saccharose, 140 g of hydroxypropylmethylcellulose and 20 g of polysorbate and wet-granulated by the addition of purified water to a suitable consistency. The granulate is then dried and standardized in terms of dimensions before the addition of a further 200 g of hydroxymethylpropylcellulose, 600 g of microcrystalline cellulose, 30 g of glycerol palmitostearate and 70 g of silicon dioxide. After mixing, the powder is sent for compression to the unit weight of 450 mg/tablet.

The cores so obtained are then subjected to film-coating with a hydroalcoholic dispersion of acrylic and methacrylic acid esters, iron oxide, talcum and triethyl citrate, which confers on the product resistance to disintegration in an acidic environment. The dissolution of the tablets is practically zero in pH conditions of less than 7 and is progressive in an enteric buffer at pH 7.2 with the following percentage quotas:

- less than 25% within the first hour of residence,
- more than 25% and less than 70% within the third hour of residence,
- more than 80% after 8 hours' residence.

EXAMPLE 4

500 g of metronidazole are mixed with the components of the lipophilic/amphiphilic matrix, 5 g of stearic acid and 5 g of soya lecithin, some of the hydrophilic polymer, 100 g of hydroxypropylcellulose, and diluents, 150 g of mannitol.

The mixture is then made into a paste with a solution of low-viscosity hydroxypropylcellulose in purified water until a consistent granulate is obtained. After drying, the granulate obtained is mixed with a further 100 g of hydroxypropylcellulose, to which are added flow agents and lubricants, 5 g of silica, 5 g of talcum and 5 g of magnesium stearate, then compressed to a final weight of 925 mg/tablet. The tablets are finally coated with an alcohol-based suspension of acrylic and methacrylic copolymers capable of imparting to the

tablets efficacious gastroresistance.

The rate of dissolution of those tablets is progressive and controlled, with approximately 20% of the active ingredient being released after the first hour of residence in enteric juice at pH 7.2, 50% after 2 hours and more than 80% after 4 hours, these figures being understood as quotas that are clearly subsequent to 2 hours' exposure at pH 1 and 1 hour's exposure at pH 6.4, reflecting the environment of the stomach and of the small intestine, respectively.

CLAIMS

1. Oral pharmaceutical compositions containing at least one substance having antimicrobial and/or anti-infectious activity in association with one or more pharmacologically acceptable excipient(s), characterized in that the controlled and/or delayed release of the active ingredient takes place in the large intestine.

2. Pharmaceutical compositions according to claim 1, wherein the release of the active ingredient takes place in the colon.

3. Pharmaceutical compositions according to the preceding claims, wherein the active ingredient is rifamicin SV.

4. Pharmaceutical compositions according to the preceding claims, wherein the active ingredient is metronidazole.

5. Pharmaceutical compositions according to the preceding claims, wherein the active ingredient is contained in an amount of from 10 to 90% by weight.

6. Pharmaceutical compositions according to the preceding claims, wherein the rifamicin SV is contained in an amount of from 20 to 60% by weight.

7. Pharmaceutical compositions according to the preceding claims, wherein the metronidazole is contained in an amount of from 25 to 70% by weight.

8. Pharmaceutical compositions according to the preceding claims, wherein the controlled and/or delayed release is given by a multi-matrix structure comprising:

a) an amphiphilic matrix in which the active ingredient is incorporated;

b) a lipophilic matrix which is formed by substances having a melting point of less than 90° C and in which a) is dispersed;

c) a hydrophilic matrix.

9. Pharmaceutical compositions according to claim 8, wherein the amphiphilic matrix is selected from lecithin, polyoxyethylenated sorbitan monooleate, sodium lauryl sulphate, sodium dioctyl sulphosuccinate and/or ethylene and/or propylene block copolymers.

10. Pharmaceutical compositions according to claim 8, wherein the lipophilic matrix is selected from stearic acid, beeswax, carnauba wax, palmitic acid and/or palmitostearate esters.

11. Pharmaceutical compositions according to claim 8, wherein the hydrophilic matrix is selected from hydroxypropylcellulose, hydroxypropylmethylcellulose,

sodium carboxymethylcellulose, hydroxyethylcellulose, carboxyvinyl polymers, polyvinyl alcohol, vinyl polymers, alginic acid and its salts and/or polysaccharide polymers.

12. Pharmaceutical compositions according to the preceding claims, comprising a gastro-protective coating.

13. Pharmaceutical compositions according to claim 12, wherein the gastro-protective coating is selected from acrylic and methacrylic acid esters and/or cellulose acetate phthalate.

14. Pharmaceutical compositions according to the preceding claims for the treatment of pathologies of the large intestine.

15. Pharmaceutical compositions according to the preceding claims for the treatment of pathologies of the colon.

16. Pharmaceutical compositions according to the preceding claims for the treatment of infectious colites, bacillary dysentery, pseudomembranous colitis, travellers' diarrhoea, diverticular disease and/or diverticulitis.

17. Pharmaceutical compositions according to the preceding claims for preparation treatment for surgical operations on the colon and/or for support treatment in the therapy of ammonaemias or hyperammonaemias.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/052025

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/26 A61K9/32 A61K31/395 A61K31/4164

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)
IPC 7 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 practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 793 959 A (TAKEDA CHEMICAL INDUSTRIES, LTD) 10 September 1997 (1997-09-10) column 1, line 58 - column 2, line 13; examples	1,2,4
X	US 5 849 327 A (BERLINER ET AL) 15 December 1998 (1998-12-15) examples	1,2,4
X	WO 00/25756 A (DR. FALK PHARMA GMBH; OTTERBECK, NORBERT; KIST, MANFRED) 11 May 2000 (2000-05-11) examples	1,2,4

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

[X] Patent family members are listed in 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 document 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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 2005	03/08/2005

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giménez Miralles, J

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/030173 A (RANBAXY LABORATORIES LIMITED; WILSON, CLIVE; MUKHERJI, GOUR; RAMPAL, A) 7 April 2005 (2005-04-07) claim 3	1,2,4
Y	EP 1 183 014 A (COSMO S.P.A) 6 March 2002 (2002-03-06) cited in the application column 6, line 24 - line 26; examples	1-17
Y	GB 2 245 492 A (* ZAMBON GROUP S.P.A) 8 January 1992 (1992-01-08) cited in the application examples	1-17
Y	EP 0 572 942 A (POLI INDUSTRIA CHIMICA S.P.A; MONSANTO ITALIANA S.P.A; POLICHEM S.A) 8 December 1993 (1993-12-08) cited in the application examples	1-17
Y	WO 2004/017962 A (S.L.A. PHARMA AG; ARMSTRONG, DAVID, NIGEL) 4 March 2004 (2004-03-04) the whole document	1-17
Y	EP 0 366 621 A (ISTITUTO DE ANGELI S.P.A) 2 May 1990 (1990-05-02) abstract	1-17
Y	GB 2 352 172 A (* WEST PHARMACEUTICAL SERVICES DRUG DELIVERY & CLINICAL RESEARCH CENTR) 24 January 2001 (2001-01-24) examples	1-17
Y	US 5 985 823 A (GOLDSTEIN ET AL) 16 November 1999 (1999-11-16) examples	1-17
Y	WO 01/11077 A (CEDARS-SINAI MEDICAL CENTER) 15 February 2001 (2001-02-15) cited in the application page 19, line 12 - line 24	1-17
Y	DATABASE WPI Section Ch, Week 200346 Derwent Publications Ltd., London, GB; Class B03, AN 2003-483136 XP002337500 & CN 1 398 587 A (ANHUI PROV INST PHARMACOLOGY) 26 February 2003 (2003-02-26) abstract	1-17

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Section Ch, Week 199719 Derwent Publications Ltd., London, GB; Class B03, AN 1997-204067 XP002337501 & CN 1 097 306 A (UNIV CHINA MEDICAL CLINICS COLLEGE NO 2) 18 January 1995 (1995-01-18) abstract	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/052025

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1 (partially)

Present claim 1 relates to an extremely large number of possible oral pharmaceutical compositions, namely all those comprising an antimicrobial agent and an excipient, with no limitation or restriction, wherein the subject-matter is defined in terms of the result to be achieved, namely that release of the active agent takes place in sustained manner in the large intestine and/or colon.

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compositions falling within the scope of claim 1, namely enterically coated tablets comprising a particular granulation in the tablet core, i.e. the subject-matter of claims 8-13. Indeed, the features defined in these claims are essential for achieving the result claimed in claim 1 (large intestine/colon delivery). In the present case, claim 1 so lack support, or the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the subject-matter of present claim 1 taken in combination with claims 8-13, as construed in the light of the description and the examples.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

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