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US 09/539,982 (CON)
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(54) Title: CAMPTOTHECIN COMPLEXES

(57) Abstract: Disclosed are compositions that include a camptothecin and an amorphous cyclodextrin. The camptothecin may be substituted or unsubstituted. Also disclosed are methods of treating undesirable or uncontrolled cell proliferation by administering the inventive compositions. Finally, implants including an implant structure and the inventive composition are disclosed.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/06829

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K47/48 A61K31/4745

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)

MEDLINE, EMBASE, EPO-Internal, BIOSIS, DISSERTATION ABS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	UNDERBERG WJ ET AL: "Equilibrium kinetics of the new experimental anti-tumour compound SK&F 104864-A in aqueous solution." JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, 1990, VOL. 8, NO. 8-12, PAGE(S) 681-3, XP001053447	1-28,41
Y	page 681 -page 681, left-hand column, line 7 tables 1,2 page 683, right-hand column, last paragraph --- -/--	29-40

☒ Further documents are listed in the continuation of box C.

☒ 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
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- *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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/06829

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SHARMA U S ET AL: "PHARMACEUTICAL AND PHYSICAL PROPERTIES OF PACLITAXEL (TAXOL) COMPLEXES WITH CYCLODEXTRINS" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 84, no. 10, 1 October 1995 (1995-10-01), pages 1223-1230, XP000529731 ISSN: 0022-3549 cited in the application abstract figures 1-5 tables 1,2 ---	1-28,41
Y	JONKMAN-DE VRIES J.D. ET AL: "Pharmaceutical development of (investigational) anticancer agents for parenteral use - A review" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 1996, VOL. 22, NO. 6, PAGE(S) 475-494, XP001053466 page 482, left-hand column, line 15 - line 39 ---	1-28,41
Y	WO 99 62510 A (ANGIOTECH PHARM INC ;HUNTER WILLIAM L (CA)) 9 December 1999 (1999-12-09) examples 13,24,62 ---	1-41
E	US 2001/021703 A1 (KOSAK KENNETH M) 13 September 2001 (2001-09-13) paragraph '0200! - paragraph '0202! ---	1-28,41
Y	GIOVANELLA B C ET AL: "Protocols for the treatment of human tumor xenografts with camptothecins." ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 803, 1996, pages 181-187, XP001053591 Conference;Bethesda, Maryland, USA; February 7-10, 1996, discovery to the patient. 1996 New York Academy of Sciences 2 East 63rd Street, New York, New York 10021, USA ISBN: 1-57331-057-3 page 181, paragraph INTRODUCTION page 184, paragraph -page 186 --- -/--	1-41

INTERNATIONAL SEARCH REPORT

International Application No

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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.
Y	SAIJO NAGAHIRO: "Clinical trials of irinotecan hydrochloride (CPT, campto injection, topotecan injection) in Japan." ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 803, 1996, pages 292-305, XP001053587 Conference; Bethesda, Maryland, USA; February 7-10, 1996, discovery to the patient. 1996 New York Academy of Sciences 2 East 63rd Street, New York, New York 10021, USA ISBN: 1-57331-057-3 page 292, paragraph INTRODUCTION figures 1-3 tables 1,2 page 300, paragraph DISCUSSION -page 301 ---	1-41
Y	FRIEDMAN HENRY S ET AL: "Treatment of central nervous system xenografts with camptothecins." ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 803, 1996, pages 210-212, XP001053589 Conference; Bethesda, Maryland, USA; February 7-10, 1996, discovery to the patient. 1996 New York Academy of Sciences 2 East 63rd Street, New York, New York 10021, USA ISBN: 1-57331-057-3 the whole document ---	1-41
Y	NATELSON ETHAN A ET AL: "Phase I clinical and pharmacological studies of 20-(S)-camptothecin and 20-(S)-9-nitrocamptothecin as anticancer agents." ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 803, 1996, pages 224-230, XP001053588 Conference; Bethesda, Maryland, USA; February 7-10, 1996, discovery to the patient. 1996 New York Academy of Sciences 2 East 63rd Street, New York, New York 10021, USA ISBN: 1-57331-057-3 the whole document ---	1-41
Y	EP 0 623 354 A (MEDTRONIC INC) 9 November 1994 (1994-11-09) the whole document	29-40
Y	& US 5 464 650 A (E.P. BERG ET AL.) 7 November 1995 (1995-11-07) cited in the application --- -/--	29-40

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/06829

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 30684 A (SUPERGEN INC) 24 June 1999 (1999-06-24) examples ---	29-40
Y	WO 00 00238 A (QUANAM MEDICAL CORP) 6 January 2000 (2000-01-06) examples 2-4 -----	29-40

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-41 in part, and 42

The problem underlying the present application is to provide new forms of camptothecin derivatives for administration. As solution to this problem, their inclusion complexes with cyclodextrins are proposed. These inclusion complexes are also claimed to be used for coating certain devices, e.g., stents.

The technical feature, linking these solutions together, is the inclusion complex of the camptothecin derivatives with cyclodextrins.

This common part is already known in the prior art:

UNDERBERG WJ ET AL: "Equilibrium kinetics of the new experimental anti-tumour compound SK&F 104864-A in aqueous solution." JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, 1990, VOL. 8, NO. 8-12, PAGE(S) 681-3. XP001053447 describes the stabilisation of 9-dimethylaminomethyl, 10-hydroxy-camptothecin by a number of cyclodextrins. Of the cyclodextrins tested, dimethyl- cyclodextrin appears to be the most efficient.

For this reason, the technical feature mentioned above can no longer be accepted as special technical feature linking the different inventions together. Since there is no other technical feature that could fulfil the role of special technical feature in the sense of Rule 13.2 PCT, the present application is found to lack unity of invention.

Insofar as compositions containing camptothecin derivatives with cyclodextrins are concerned, there is no further technical feature which would be acceptable as a special technical feature in the sense of Rule 13.2 PCT. Therefore, in principle, each of the complexes specifically represents a different subject.

For the implants or stents, the application of an inclusion complex of camptothecin derivatives with cyclodextrins to such devices has not been described, and could therefore be construed as the special technical feature in the sense of Rule 13.2 PCT linking these inventions together. As a result, the present application is found to contain the subjects as mentioned.

However, since it is felt by the International Searching Authority, that the inventions 2-6 do not fulfil the requirements of Articles 5 and 6 PCT, it would be useless to issue an invitation to pay a additional search fees.

Present claims 1-41 relate to an extremely large number of possible compositions, and to devices or methods in which these compositions are used. 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 claimed. Moreover, the formation of an inclusion complex seems to be essential to the invention, whereas this feature is absent from claims 1-28. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

A similar objection must be raised for the implants defined in claims 29-34, and for the stent according to claims 36-39.

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 compositions prepared in the examples and to those

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compositions mentioned specifically in the claims.
Claim 42 does not contain technical features, and is therefore considered unsearchable.

The applicant's attention is drawn to the fact that claims, or parts of 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-28 and 41 in part

Compositions containing an inclusion complex of a camptothecin derivative and a cyclodextrin, insofar as not mentioned in subjects 2-6.

2. Claims: 1-28 and 41 in part

Compositions containing an inclusion complex of 9-nitrocamptothecin and a cyclodextrin, and method as claimed, using these compositions.

3. Claims: 1-28 and 41 in part

Compositions containing an inclusion complex of 9-aminocamptothecin and a cyclodextrin, and method as claimed, using these compositions.

4. Claims: 1-28 and 41 in part

Compositions containing an inclusion complex of 10,11-methylenedioxy-20(S)-camptothecin and a cyclodextrin, and method as claimed, using these compositions.

5. Claims: 1-28 and 41 in part

Compositions containing an inclusion complex of 7-ethyl-10-hydroxy-camptothecin and a cyclodextrin, and method as claimed, using these compositions.

6. Claims: 29-41

Implants or stents containing an inclusion complex of a camptothecin derivative and a cyclodextrin, and method as claimed, using these compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/06829

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			DE 69900689 D1	21-02-2002
			EP 1087801 A1	04-04-2001
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