

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
10 January 2002 (10.01.2002)

PCT

(10) International Publication Number  
**WO 02/02146 A3**

(51) International Patent Classification<sup>7</sup>: **A61K 47/48**

(21) International Application Number: PCT/GB01/02886

(22) International Filing Date: 2 July 2001 (02.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0016134.9 1 July 2000 (01.07.2000) GB  
0022156.4 9 September 2000 (09.09.2000) GB

(71) Applicant (for all designated States except US): **ML LABORATORIES PLC** [GB/GB]; 17 Hanover Square, London W1R 9AJ (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SHAUNAK, Sunil** [GB/GB]; 117 Ware Road, Hertford, Hertfordshire SG13 7EE (GB). **DUNCAN, Ruth** [GB/GB]; School of Pharmacy, Cardiff University, Redwood Building, King Edward VII Avenue, Cardiff CF10 3XF (GB). **GERMAN, Lisa** [GB/GB]; White Barn, St. Julian's Farm, Old St. Mellons, Cardiff CF3 9YJ (GB). **HRECZUK-HIRST, Dale** [GB/GB]; 8 Albany Road, Reading Berkshire RG30 2VN (GB).

(74) Agent: **HARRISON GODDARD FOOTE**; 31 St. Saviourgate, York YO1 8NQ, Leeds LS2 8PA (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

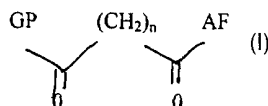
**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
13 June 2002

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: DEXTRIN-AMPHOTERICIN CONJUGATES AND THEIR METHODS OF PREPARATION



(57) Abstract: There is described a compound of the general formula (I); wherein GP is a glucose polymer, or a mixture of glucose polymers, and optionally salts thereof; AF is an antifungal agent; and n is an integer from 1 to 12. There is also described compositions containing this compound and methods of treatment relating thereto.



Dextrin- AmpB at 0.5 mg/ml

WO 02/02146 A3

## INTERNATIONAL SEARCH REPORT

International Application No

PC1, GB 01/02886

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K47/48

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, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                 | Relevant to claim No. |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| P,X        | GERMAN L A ET AL: "Dextrin-amphotericin B: A potential polymeric anti-infective or antiparasitic agent."<br>JOURNAL OF PHARMACY AND PHARMACOLOGY,<br>vol. 52, no. Supplement,<br>September 2000 (2000-09), page 37<br>XP001022489<br>137th British Pharmaceutical<br>Conference; Birmingham, England, UK;<br>September 10-13, 2000<br>ISSN: 0022-3573<br>the whole document<br>--- | 1-12,27,<br>29,31-37  |
| X          | WO 98 56424 A (CASSIDY JAMES ;DUNCAN RUTH<br>(GB); GERMAN LISA (GB); HIRST DALE (GB))<br>17 December 1998 (1998-12-17)                                                                                                                                                                                                                                                             | 1,7-12,<br>31-36      |
| Y          | page 4, line 16-26; claims; figures 3A,3B;<br>examples<br>---                                                                                                                                                                                                                                                                                                                      | 1-12,27,<br>29,31-37  |
|            | -/--                                                                                                                                                                                                                                                                                                                                                                               |                       |

☒ 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

"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.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

13 November 2001

Date of mailing of the international search report

03. 04. 02

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

Authorized officer

Veronese, A

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/02886

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                          | Relevant to claim No. |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A          | YOUNG D H ET AL: "ANTIFUNGAL PROPERTIES OF TAXOL AND VARIOUS ANALOGUES" EXPERIENTIA, BIRKHAUSER VERLAG. BASEL, CH, vol. 48, no. 9, 1992, pages 882-885, XP000929422<br>ISSN: 0014-4754<br>the whole document                                                                                                                                                                                                                                | 1,7-12,<br>32-36      |
| X          | ---<br>DUNCAN R ET AL: "Dextrins as Carriers of Anticancer Agents" PROCEEDINGS OF THE 24TH. INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS. STOCKHOLM, JUNE 15 - 19, 1997, PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS, DEERFIELD, IL., CONTROLLED RELEASE, vol. SYMP. 24, 15 June 1997 (1997-06-15), pages 771-772, XP002078115<br>ISSN: 1022-0178<br>the whole document | 35,36                 |
| Y          | ---<br>FALK RAMA ET AL: "A novel injectable water-soluble amphotericin B-arabinogalactan conjugate." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 43, no. 8, August 1999 (1999-08), pages 1975-1981, XP002182534<br>ISSN: 0066-4804<br>page Y                                                                                                                                                                                                | 1-12,27,<br>29,31-37  |
| Y          | ---<br>WO 90 15628 A (CETUS CORP)<br>27 December 1990 (1990-12-27)<br>claims 7,21                                                                                                                                                                                                                                                                                                                                                           | 1-12,27,<br>29,31-37  |
| A          | ---<br>EP 0 466 038 A (SQUIBB & SONS INC)<br>15 January 1992 (1992-01-15)<br>the whole document<br>-----                                                                                                                                                                                                                                                                                                                                    | 1                     |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 01/02886

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.:  
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

see additional sheet

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.:  
  
27 (partial); 1-12, 29, 31-37 (complete

### 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 I.2

Present claims 1-12, 27, 29, 31-37 relate to an extremely large number of possible compounds. In the present case it is not possible from formula (I) to determine how and in which position the polymer and the antifungal agent are linked to the spacer; therefore a lack of clarity exists in the sense of art 6 PCT. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, for only a very small proportion of the compounds claimed. 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. 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 compounds of the general formula I in which the glucose polymer is a dextrin, (in particular 1,4 glucose dextrans) and the antifungal agent is a polyene antibiotic, (in particular amphotericin and nystatin). Accordingly, the search for claims 35-37 has been restricted to the dextrin derivatives.

Claim 31, which covers the use of any glucose polymer in the manufacture of a medicament for the treatment of fungal infections, is supported only for those parts related to derivatives in which the glucose polymer is conjugated to an antifungal agent as shown in the compounds of formula I in claim 1. The search has therefore only covered this part of the claim.

Moreover, claim 27 relates to a compound defined by reference to a desirable characteristic or property, namely a certain solubility in water. The claim covers all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. 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. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I) with the restrictions which have already indicated above.

Claims 1-12, 27, 29, 31-37 have been searched partially.

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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: 27 (partial); 1-12,29, 31-37 (complete).

Compounds having the general formula I as shown in claim 1, their method of preparation as well as the intermediate derivatives disclosed in claims 32-37, and their use in relation to the treatment of fungal infections.

2. Claims: 27 (partial); 13-26, 28, 30 (complete).

Pharmaceutical compositions comprising a complex of an antifungal agent and a glucose polymer.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/02886

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)                                      | Publication<br>date                                  |
|-------------------------------------------|---------------------|-----------------------------------------------------------------|------------------------------------------------------|
| WO 9856424 A                              | 17-12-1998          | AU 8025998 A<br>EP 0998303 A1<br>WO 9856424 A1<br>US 6338843 B1 | 30-12-1998<br>10-05-2000<br>17-12-1998<br>15-01-2002 |
| WO 9015628 A                              | 27-12-1990          | AU 5858690 A<br>CA 2018833 A1<br>WO 9015628 A1                  | 08-01-1991<br>14-12-1990<br>27-12-1990               |
| EP 0466038 A                              | 15-01-1992          | CA 2044663 A1<br>EP 0466038 A1<br>JP 4230324 A                  | 13-01-1992<br>15-01-1992<br>19-08-1992               |