(19) World Intellectual Property Organization International Bureau





(43) International Publication Date 21 November 2002 (21.11.2002)

(10) International Publication Number WO 02/092062 A3

(51) International Patent Classification7: A61K 31/00

(21) International Application Number: PCT/DK02/00317

(22) International Filing Date: 15 May 2002 (15.05.2002)

English (25) Filing Language:

(26) Publication Language: English

(30) Priority Data:

PA 2001 00759 15 May 2001 (15.05.2001)

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(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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, 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, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

with international search report

(88) Date of publication of the international search report: 13 February 2003

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: COMBINATION OF VITAMIN D ANALOGUE AND PYRIMIDINE NUCLEOSIDE ANALOGUE

(57) Abstract: The present invention relates to a pharmaceutical composition comprising a vitamin D analogue capable of upregulating the expression of cytidine deaminase in tumour cells and a cytostatic pyrimidine nucleoside analogue and its use in a combination treatment of neoplastic diseases.

International Application No PCT/DK 02/00317

a. classification of subject matter IPC 7 A61K31/00

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) I PC $\,\,7\,$ A61K $\,$ C07C

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

	ENTS CONSIDERED TO BE RELEVANT	Deleventa de S	
ategory °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
>,χ	WO 01 37808 A (LIPOCINE INC) 31 May 2001 (2001-05-31) specially claim 5 and claim 9 claims 1-38	1-37	
(WO 01 34133 A (LILLY CO ELI (US)) 17 May 2001 (2001-05-17) specially claim 4, line 15.	1-37	
Y	VERWEIJ J: "Rational design of new tumoractivatedTM cytotoxic agents." ONCOLOGY, vol. 57(suppl 1), 1999, pages 9-15, XP002902600 the whole document	1-37	
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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 5 August 2002	Date of mailing of the international search report 15. 11. 2002		
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 Fernando Farieta		

International Application No
PCT/DK 02/00317

	TO DE DE L'ANTE	1 101/01 02/00317					
	Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.						
Jalegury	Oracion of Goodfield, with indication, where appropriately of the following passages						
Y	MEJER J N ET AL: "Modulation of the effect of 1-beta-D-arabinofuranosylcytosine based on changes of cytidine deaminase activity in HL60 cells." MED. ONCOLOGY & TUMOR PHARMACOTHER., vol. 7, no. 1, 1990, pages 25-29, XP002902601 the whole document	1-37					
A	WO 95 02577 A (LEO PHARM PROD LTD) 26 January 1995 (1995-01-26) claims 1-11	1-37					
Α	WO 91 00855 A (LEO PHARM PROD LTD) 24 January 1991 (1991-01-24) claims 1-13	1-37					
A	TOMOO FUNAKI ET AL: "Simultaneous determination of a new anticancer drug galocitabine and its metabolites in blood by high-performance liquid chromatography." JOURNAL OF PHARMACEUTICAL & BIOMEDICAL ANALYSIS, vol. 11, no. 4/5, 1993, pages 379-384, XP002902602 the whole document	1-37					
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International application No. PCT/DK 02/00317

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: 25-31 because they relate to subject matter not required to be searched by this Authority, namely: see FURTHER INFORMATION sheet PCT/ISA/210
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:
з	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 Inte	ernational 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. X	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.: 1-37
Remark	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.1

Claims Nos.: 25-31

Claim 25-31 relate to a method for treatment of the human or animal body by therapy/ diagnostic methods practised on the human or animal body/ Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compositions.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 1-37

A composition, pharmaceutical combination, nuse of a vitamin D analogue and a cytostatic pyrimidine nucleoside and a method there of, according to claims 1-24 and 32-37.

2. Claims: 38-42

A method of screening for vitamin D analogues activity as upregulating the expression of cytidine deaminase compare to vitamin D3, according to claims 38-42.

Information on patent family members

Intermional Application No
PCT/DK 02/00317

Patent document cited in search report WO 0137808	A	Publication date		Patent family member(s)	Publication date
WO 0137808	Α	21 05 0001			
		31-05-2001	US AU EP WO	6248363 B1 1798101 A 1233756 A1 0137808 A1	19-06-2001 04-06-2001 28-08-2002 31-05-2001
WO 0134133	Α	17-05-2001	AU WO	1595001 A 0134133 A2	06-06-2001 17-05-2001
WO 9502577	A	26-01-1995	AT AU CA CN DE DE WO EP ES FI JP NZ RU US	165346 T 690564 B2 7182994 A 2162040 A1 1125941 A ,B 69409811 D1 69409811 T2 9502577 A1 0708755 A1 2117281 T3 956108 A 8512327 T 268567 A 2130926 C1 5716945 A	15-05-1998 30-04-1998 13-02-1995 26-01-1995 03-07-1996 28-05-1998 07-01-1995 01-05-1996 01-08-1998 19-12-1995 24-12-1996 24-11-1997 27-05-1999 10-02-1998
WO 9100855	Α	24-01-1991	AT AU CA DE WO DK EP ES FI JP KR VZ PH US ZA	112556 T 630227 B2 6156390 A 2057048 A1 69013155 D1 69013155 T2 9100855 A1 482100 T3 0482100 A1 2064749 T3 93724 B 902317 A1 2807087 B2 4506965 T 195547 B1 234326 A 27301 A 5190935 A 9005094 A	15-10-1994 22-10-1992 06-02-1991 11-01-1991 10-11-1994 09-03-1995 24-01-1991 07-11-1994 29-04-1992 01-02-1995 15-02-1995 16-01-1991 30-09-1998 03-12-1992 15-06-1999 26-03-1993 04-05-1993 02-03-1993
				WO 9502577 A 26-01-1995 AT AU AU CA CN DE DE WO EP ES FI JP NZ RU US AU CA DE DE WO CA DE DE WO CA DE DE WO DK EP ES FI IE JP JP KR NZ PH US	WO 9502577 A 26-01-1995 AT 165346 T AU 690564 B2 AU 7182994 A CA 2162040 A1 CN 1125941 A ,B DE 69409811 D1 DE 69409811 T2 WO 9502577 A1 EP 0708755 A1 ES 2117281 T3 FI 956108 A JP 8512327 T NZ 268567 A RU 2130926 C1 US 5716945 A WO 9100855 A 24-01-1991 AT 112556 T AU 630227 B2 AU 6156390 A CA 2057048 A1 DE 69013155 D1 DE 69013155 D1 DE 69013155 T2 WO 9100855 A1 DK 482100 A1 ES 2064749 T3 FI 93724 B IE 902317 A1 JP 2807087 B2 JP 4506965 T KR 195547 B1 NZ 234326 A PH 27301 A US 5190935 A