



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/66	A3	(11) International Publication Number: WO 00/03677 (43) International Publication Date: 27 January 2000 (27.01.00)						
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> (21) International Application Number: PCT/IL99/00387 (22) International Filing Date: 14 July 1999 (14.07.99) (30) Priority Data: 125336 14 July 1998 (14.07.98) IL (71) Applicants (for all designated States except US): YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; Jabotinsky Street 46, 92182 Jerusalem (IL). HADASIT MEDICAL RESEARCH SERVICES & DEVELOPMENT LIMITED [IL/IL]; P.O. Box 12000, Kiryat Hadassah, Jerusalem 91120 (IL). (72) Inventors; and (75) Inventors/Applicants (for US only): GOLOMB, Gershon [IL/IL]; Tirosh Street 20, 90435 Efrat (IL). DANEBERG, Haim [IL/IL]; 47 Dulcin Street, Jerusalem 96407 (IL). (74) Agent: REINHOLD COHN AND PARTNERS; P.O. Box 4060, 61040 Tel Aviv (IL). </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 4 May 2000 (04.05.00) </td> </tr> </table>			(21) International Application Number: PCT/IL99/00387 (22) International Filing Date: 14 July 1999 (14.07.99) (30) Priority Data: 125336 14 July 1998 (14.07.98) IL (71) Applicants (for all designated States except US): YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; Jabotinsky Street 46, 92182 Jerusalem (IL). HADASIT MEDICAL RESEARCH SERVICES & DEVELOPMENT LIMITED [IL/IL]; P.O. Box 12000, Kiryat Hadassah, Jerusalem 91120 (IL). (72) Inventors; and (75) Inventors/Applicants (for US only): GOLOMB, Gershon [IL/IL]; Tirosh Street 20, 90435 Efrat (IL). DANEBERG, Haim [IL/IL]; 47 Dulcin Street, Jerusalem 96407 (IL). (74) Agent: REINHOLD COHN AND PARTNERS; P.O. Box 4060, 61040 Tel Aviv (IL).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 4 May 2000 (04.05.00)				
(21) International Application Number: PCT/IL99/00387 (22) International Filing Date: 14 July 1999 (14.07.99) (30) Priority Data: 125336 14 July 1998 (14.07.98) IL (71) Applicants (for all designated States except US): YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; Jabotinsky Street 46, 92182 Jerusalem (IL). HADASIT MEDICAL RESEARCH SERVICES & DEVELOPMENT LIMITED [IL/IL]; P.O. Box 12000, Kiryat Hadassah, Jerusalem 91120 (IL). (72) Inventors; and (75) Inventors/Applicants (for US only): GOLOMB, Gershon [IL/IL]; Tirosh Street 20, 90435 Efrat (IL). DANEBERG, Haim [IL/IL]; 47 Dulcin Street, Jerusalem 96407 (IL). (74) Agent: REINHOLD COHN AND PARTNERS; P.O. Box 4060, 61040 Tel Aviv (IL).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 4 May 2000 (04.05.00)							
(54) Title: USE OF BISPHOSPHONATES IN THE TREATMENT OF VASCULAR RESTENOSIS <table border="1" style="margin: 10px auto; border-collapse: collapse;"> <caption>NEointima/Media Ratio Data</caption> <thead> <tr> <th>Group</th> <th>NEointima/Media Ratio (approx.)</th> </tr> </thead> <tbody> <tr> <td>CLODRONATE LIPOSOMES</td> <td>0.3</td> </tr> <tr> <td>CONTROL LIPOSOMES</td> <td>1.5</td> </tr> </tbody> </table>			Group	NEointima/Media Ratio (approx.)	CLODRONATE LIPOSOMES	0.3	CONTROL LIPOSOMES	1.5
Group	NEointima/Media Ratio (approx.)							
CLODRONATE LIPOSOMES	0.3							
CONTROL LIPOSOMES	1.5							
(57) Abstract Bisphosphonate (BP), pyrophosphate (PP) a complex of BP or PP, a polymer of BP or PP or a pharmaceutically acceptable salt or ester thereof, are used for the prevention or treatment of vascular restenosis.								

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

INTERNATIONAL SEARCH REPORT

Int. lional Application No

PCT/IL 99/00387

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/66

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 38998 A (MERCK AND CO. INC.) 5 August 1999 (1999-08-05) page 2, line 16 - line 25 page 12, line 30 -page 16, line 24; claims 8,11,12 ---	1-4, 10-13, 18-21
P,X	WO 98 31359 A (MERCK AND CO. INC.) 23 July 1998 (1998-07-23) page 3, line 18 - line 23 page 26, line 7 -page 27, line 6 page 29, line 13 - line 31 ---	1-8, 10-24
X	WO 97 43437 A (THE UNIVERSITY OF SHEFFIELD) 20 November 1997 (1997-11-20) page 20, line 5-15 page 27, line 10 -page 29, line 5 --- -/--	1-5,8, 10-22,25



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.

"&" document member of the same patent family

Date of the actual completion of the international search

8 February 2000

Date of mailing of the international search report

29/02/2000

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

Mair, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 99/00387

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 33552 A (WALLACE TECHNOLOGIES INC.) 18 September 1997 (1997-09-18) page 3, line 21 - line 25 page 6, line 4 - line 16 page 9, line 11 -page 10, line 13 ---	1-5, 8-14, 16-22
X	DAOUD, A.S. ET AL: "The effect of ethane-1-hydroxy-1,1-diphosphonate (EHDP) on necrosis of atherosclerotic lesions" ATHEROSCLEROSIS, vol. 67, no. 1, 1987, pages 41-48, XP000874378 the whole document ---	1-4,8, 10-12, 16,18-20
X	WAGNER, W.D. ET AL: "Contrasting effects of ethane-1-hydroxy-1,1-diphosphonate (EHDP) on the regression of two types of dietary-induced atherosclerosis" ATHEROSCLEROSIS, vol. 27, no. 4, 1977, pages 419-436, XP000874381 the whole document ---	1-4,8, 10-12, 16,18-20
X	WEBB, C.L. ET AL: "Inhibition of bioprosthetic heart valve calcification with aminodiphosphonate covalently bound to residual aldehyde groups" THE ANNALS OF THORACIC SURGERY, vol. 46, no. 3, 1988, pages 309-316, XP000874363 the whole document ---	1-3,7, 10-14, 17-22,24
X	BELLAH, R.D. ET AL: "Idiopathic arterial calcification of infancy: Prenatal and postnatal effects of therapy in an infant" THE JOURNAL OF PEDIATRICS, vol. 121, no. 6, 1992, pages 930-933, XP000874377 the whole document especially page 933, lefthand column, line 46 ---	1,10,18
X	SHIOI, A. ET AL: "Beta-Glycerophosphate accelerates calcification in cultured bovine vascular smooth muscle cells" ARTERIOSCLEROSIS, THROMBOSIS AND VASCULAR BIOLOGY, vol. 15, no. 11, 1995, pages 2003-2009, XP000874393 abstract page 2003, left-hand column, line 10-13 page 2007; figure 8 --- -/--	1-3, 10-12

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/IL 99/00387

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PASPALIARIS, V. ET AL: "Clodronate inhibits contraction and prevents the action of L-type calcium channel antagonists in vascular smooth muscle" JOURNAL OF BONE AND MINERAL RESEARCH, vol. 6, no. 8, 1991, pages 835-841, XP000874364 the whole document ----	1-26
A	EP 0 339 237 A (SYMPHAR S.A.) 2 November 1989 (1989-11-02) the whole document ----	1-25
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US AN: 000076062622, XP002130040 abstract & KUNITOMO, M. ET AL: "Experimental induction of atherosclerosis in guinea-pigs fed a cholesterol vitamin D2 rich diet" FOLIA PHARMACOLOGICA JAPONICA, vol. 81, no. 4, 1983, pages 275-284, -----	1-25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL 99/ 00387

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:
Remark: Although claim(s) 10-17
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
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:

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 I.2

Present claims 1-2, 4-11, 13-19 and 21-25 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, 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 mentioned in claims 3, 12 and 20 and the general idea underlying the application.

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IL 99/00387

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9938998	A	05-08-1999	AU 2487899 A	16-08-1999
WO 9831359	A	23-07-1998	AU 6023198 A	07-08-1998
WO 9743437	A	20-11-1997	AU 2783397 A	05-12-1997
			EP 0952834 A	03-11-1999
WO 9733552	A	18-09-1997	AU 2580697 A	01-10-1997
			CA 2250295 A	18-09-1997
			CN 1217662 A	26-05-1999
			CZ 9802908 A	14-07-1999
			EP 0932399 A	04-08-1999
			NO 984210 A	11-11-1998
			PL 328807 A	15-02-1999
			US 5977163 A	02-11-1999
EP 339237	A	02-11-1989	CH 675422 A	28-09-1990
			AT 84040 T	15-01-1993
			AU 3224389 A	05-10-1989
			CA 1338495 A	30-07-1996
			CN 1036772 A, B	01-11-1989
			CN 1086820 A	18-05-1994
			DK 148189 A	17-10-1989
			ES 2011210 T	01-01-1994
			FI 891538 A, B,	01-10-1989
			GR 90300002 T	07-06-1991
			GR 3007442 T	30-07-1993
			HU 50482 A, B	28-02-1990
			IE 62692 B	22-02-1995
			IL 89649 A	31-07-1995
			JP 2022285 A	25-01-1990
			JP 8022865 B	06-03-1996
			KR 147830 B	17-08-1998
			NO 891317 A	02-10-1989
			NZ 228516 A	21-12-1990
			PH 27603 A	31-08-1993
			PT 90175 A, B	10-11-1989
			US 5043330 A	27-08-1991
			US 5128331 A	07-07-1992
			ZW 3789 A	23-08-1989