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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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12 August 2010

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(54) **Title**: POLYMERIC COMPOSITION WITH SYNERGISTIC EFFECT IN TREATMENT OF TUMOUR DISEASES

(57) **Abstract**: By mixing two polymeric conjugates of doxorubicin which differ in the mode of causing death of tumour cells in an appropriate ratio, synergy in an anti-tumour effect can be achieved, and such a composition is a particularly effective agent for treatment of tumour diseases.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2009/000115

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61P35/00
ADD.

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)
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, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KOVAR LUBOMIR ET AL: "The same drug but a different mechanism of action: Comparison of free doxorubicin with two different N-(2-hydroxypropyl)methacrylamide copolymer-bound doxorubicin conjugates in EL-4 cancer cell line" BIOCONJUGATE CHEMISTRY, vol. 18, no. 3, May 2007 (2007-05), pages 894-902, XP002586382 ISSN: 1043-1802 cited in the application abstract page 895, column 2, paragraph 2 - paragraph 7 page 899, column 2, paragraph 4 - page 901, column 1, paragraph 3 ----- -/--	1-9

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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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	RHOVA B ET AL: "Doxorubicin bound to a HPMA copolymer carrier through hydrazone bond is effective also in a cancer cell line with a limited content of lysosomes" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL LNKD- DOI:10.1016/S0168-3659(01)00320-0, vol. 74, no. 1-3, 6 July 2001 (2001-07-06) , pages 225-232, XP004297527 ISSN: 0168-3659 cited in the application abstract figures 1-2 page 230, column 2, paragraph 3 - page 231, column 1, paragraph 1	1-9
Y	WO 03/053473 A2 (LECIVA A S [CZ]; ULBRICH KAREL [CZ]; ETRYCH TOMAS [CZ]; RIHOVA BLANKA) 3 July 2003 (2003-07-03) examples 1-9 figures 1,3,6,7	1-9
Y	KOVAR M ET AL: "HPMA copolymers containing doxorubicin bound by a proteolytically or hydrolytically cleavable bond: comparison of biological properties in vitro" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL LNKD- DOI:10.1016/J.JCONREL.2004.07.015, vol. 99, no. 2, 30 September 2004 (2004-09-30), pages 301-314, XP004569550 ISSN: 0168-3659 cited in the application abstract page 310, column 1, paragraph 2 - page 312, column 1, paragraph 3	1-9

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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	SIROVA M ET AL: "TREATMENT WITH HPMA COPOLYMER-BASED DOXORUBICIN CONJUGATE CONTAINING HUMAN IMMUNOGLOBULIN INDUCES LONG-LASTING SYSTEMIC ANTI-TUMOUR IMMUNITY IN MICE" CANCER IMMUNOLOGY AND IMMUNOTHERAPY, SPRINGER-VERLAG, BERLIN, DE LNKD-DOI:10.1007/S00262-006-0168-0, vol. 56, no. 1, 1 January 2007 (2007-01-01), pages 35-47, XP019458905 ISSN: 0340-7004 cited in the application abstract figure 1 page 42, column 2, paragraph 3 - page 45, column 2, paragraph 2	1-9
Y	ULBRICH K ET AL: "HPMA copolymers with pH-controlled release of doxorubicin - In vitro cytotoxicity and in vivo antitumor activity" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL LNKD-DOI:10.1016/S0168-3659(02)00348-6, vol. 87, no. 1-3, 21 February 2003 (2003-02-21), pages 33-47, XP004412737 ISSN: 0168-3659 cited in the application abstract figure 1 page 46, column 1, paragraph 3 - column 2, paragraph 1	1-9
Y	ETRYCH T ET AL: "SYNTHESIS OF HPMA COPOLYMERS CONTAINING DOXORUBICIN BOUND VIA A HYDRAZONE LINKAGE. EFFECT OF SPACER ON DRUG RELEASE AND IN VITRO CYTOTOXICITY" MACROMOLECULAR BIOSCIENCE, WILEY VCH VERLAG, WEINHEIM, DE LNKD-DOI:10.1002/1616-5195(20020101)2:1&LT,43::AID-MABI43&GT,3.0.CO,2-8, vol. 2, no. 1, 1 January 2002 (2002-01-01), pages 43-52, XP008076237 ISSN: 1616-5187 cited in the application abstract figure 2 page 51, column 2, paragraph 3	1-9

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International application No
PCT/CZ2009/000115

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHYTIL P ET AL: "Properties of HPMA copolymer-doxorubicin conjugates with pH-controlled activation: Effect of polymer chain modification" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL LNKD- DOI:10.1016/J.JCONREL.2006.06.028, vol. 115, no. 1, 28 September 2006 (2006-09-28), pages 26-36, XP024957636 ISSN: 0168-3659 [retrieved on 2006-09-28] abstract figure 1 page 35, column 1, paragraph 5 - column 2, paragraph 1	1-9
Y	WO 2008/034391 A1 (ZENTIVA AS [CZ]; ETRYCH TOMAS [CZ]; CHYTIL PETR [CZ]; ULBRICH KAREL [C) 27 March 2008 (2008-03-27) cited in the application examples 1-27	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2009/000115

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03053473 A2	03-07-2003	AT	439864 T	15-09-2009
		AU	2002366715 A1	09-07-2003
		CA	2470976 A1	03-07-2003
		CZ	20014653 A3	13-08-2003
		DK	1463529 T3	19-10-2009
		EP	1463529 A2	06-10-2004
		EP	1782833 A2	09-05-2007
		ES	2331303 T3	29-12-2009
		HU	0500541 A2	28-09-2005
		JP	2005519044 T	30-06-2005
		PT	1463529 E	03-11-2009
		SI	1463529 T1	29-01-2010
		SK	2912004 A3	01-12-2004
		US	2006057099 A1	16-03-2006
WO 2008034391 A1	27-03-2008	CZ	298945 B6	19-03-2008
		EA	200900453 A1	30-10-2009
		EP	2063914 A1	03-06-2009
		US	2009306004 A1	10-12-2009