



(11)

EP 1 937 310 B8

(12)

CORRECTED EUROPEAN PATENT SPECIFICATION

- (15) Correction information:
Corrected version no 2 (W2 B1)
Corrections, see
Bibliography INID code(s) 73
- (48) Corrigendum issued on:
13.07.2011 Bulletin 2011/28
- (45) Date of publication and mention
of the grant of the patent:
24.11.2010 Bulletin 2010/47
- (21) Application number: **06793626.0**
- (22) Date of filing: **19.09.2006**

(51) Int Cl.:
A61P 35/00 (2006.01) **A61K 47/48 (2006.01)**

(86) International application number:
PCT/EP2006/066489

(87) International publication number:
WO 2007/039448 (12.04.2007 Gazette 2007/15)

(54) USE OF CONJUGATES OF DOXORUBICIN WITH LACTOSAMINATED ALBUMIN

VERWENDUNG VON KONJUGATEN VON DOXORUBICIN MIT LACTOSAMINIERTEM ALBUMIN
UTILISATION DE CONJUGUES DE DOXORUBICINE ET D'ALBUMINE LACTOSAMINEE

- (84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI
SK TR**
- (30) Priority: **20.09.2005 IT MI20051743**
- (43) Date of publication of application:
02.07.2008 Bulletin 2008/27
- (73) Proprietor: **Universita' di Bologna
-Dipartimento di Patologia Sperimentale
40126 Bologna (IT)**
- (72) Inventors:
 - **FIUME, Luigi
I-40125 Bologna (IT)**
 - **DI STEFANO, Giuseppina
I-40068 San Lazzaro Di Savena (BO) (IT)**
- (74) Representative: **Pistolesi, Roberto et al
Dragotti & Associati Srl
Via Marina 6
20121 Milano (IT)**
- (56) References cited:
WO-A-93/25239 **WO-A2-2005/107814**
WO-A2-2006/074272

- **STEFANO DI G ET AL:** "Doxorubicin coupled to lactosaminated human albumin remains confined within mouse liver cells after the intracellular release from the carrier" **DIGESTIVE AND LIVER DISEASE**, W.B. SAUNDERS, vol. 35, no. 6, June 2003 (2003-06), pages 428-433, XP002361079 ISSN: 1590-8658
- **STEFANO G D ET AL:** "A novel method for coupling doxorubicin to lactosaminated human albumin by an acid sensitive hydrazone bond: synthesis, characterization and preliminary biological properties of the conjugate" **EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES**, ELSEVIER, AMSTERDAM, NL, vol. 23, no. 4-5, December 2004 (2004-12), pages 393-397, XP004658708 ISSN: 0928-0987
- **KRATZ F:** "Drug conjugates with albumin and transferrin" **EXPERT OPINION ON THERAPEUTIC PATENTS**, ASHLEY PUBLICATIONS, GB, vol. 12, no. 3, 2002, pages 433-439, XP002337252 ISSN: 1354-3776
- **SEOW Y-Y T ET AL:** "Expression of a functional asialoglycoprotein receptor in human renal proximal tubular epithelial cells" **NEPHRON**, XX, XX, vol. 91, no. 3, 2002, pages 431-438, XP008066266 ISSN: 0028-2766

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

- TRERÈ D ET AL: "THE ASIALOGLYCOPEPTIDE RECEPTOR IN HUMAN HEPATOCELLULAR CARCINOMAS: ITS EXPRESSION ON PROLIFERATING CELLS" BRITISH JOURNAL OF CANCER, LONDON, GB, vol. 81, no. 3, 1999, pages 404-408, XP008075840 ISSN: 0007-0920
- SAXENA A. ET AL: "H2, the minor subunit of the human asialoglycoprotein receptor, traffics intracellularly and forms homo-oligomers, but does not bind asialo-orosomucoid" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 38, 2002, pages 35297-35304, XP002423100
- FIUME ET AL: "Doxorubicin coupled to lactosaminated albumin inhibits the growth of hepatocellular carcinomas induced in rats by diethylnitrosamine" JOURNAL OF HEPATOLOGY, MUNKSGAARD INTERNATIONAL PUBLISHERS, COPENHAGEN, DK, vol. 43, no. 4, October 2005 (2005-10), pages 645-652, XP005058385 ISSN: 0168-8278
- DI STEFANO G ET AL: "ENHANCED UPTAKE OF LACTOSAMINATED HUMAN ALBUMIN BY RAT HEPATOCARCINOMAS: IMPLICATIONS FOR AN IMPROVED CHEMOTHERAPY OF PRIMARY LIVER TUMORS" LIVER INTERNATIONAL, BLACKWELL MUNKSGAARD, OXFORD, GB, vol. 25, no. 4, 2005, pages 854-860, XP008075833 ISSN: 1478-3223
- DI STEFANO ET AL: "Doxorubicin coupled to lactosaminated albumin: Enhanced drug levels in rat hepatocarcinomas" DIGESTIVE AND LIVER DISEASE, W.B. SAUNDERS, vol. 38, no. 4, April 2006 (2006-04), pages 284-285, XP005347320 ISSN: 1590-8658
- DI STEFANO G ET AL: "A CONJUGATE OF DOXORUBICIN WITH LACTOSAMINATED ALBUMIN ENHANCES THE DRUG CONCENTRATIONS IN ALL THE FORMS OF RAT HEPATOCELLULAR CARCINOMAS INDEPENDENTLY OF THEIR DIFFERENTIATION GRADE" LIVER INTERNATIONAL, BLACKWELL MUNKSGAARD, OXFORD, GB, vol. 26, no. 6, 2006, pages 726-733, XP008075839 ISSN: 1478-3223
- HARRIS L ET AL: "Patterns of ligand binding to normal, regenerating, preneoplastic, and neoplastic rat hepatocytes" CANCER RESEARCH 1987 US, vol. 47, no. 15, 1987, pages 3954-3958, ISSN: 0008-5472
- ASHWELL G ET AL: "CARBOHYDRATE SPECIFIC RECEPTORS OF THE LIVER" SNELL, E. E. (ED.).ANNUAL REVIEW OF BIOCHEMISTRY, VOL. 51. XII+1055P. ANNUAL REVIEWS INC.: PALO ALTO, CALIF., USA. ILLUS SERIES : ANNUAL REVIEW OF BIOCHEMISTRY (ISSN 0066-4154), 1982, pages P531-554,
- FIUME L ET AL: "Lactosaminated human serum albumin as hepatotropic drug carrier. Rate of uptake by mouse liver" FEBS LETTERS 1982 NL LNKD- DOI:10.1016/0014-5793(82)80701-1, vol. 146, no. 1, 1982, pages 42-46, ISSN: 0014-5793