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(54) Title: FORMS OF LAPATINIB DITOSYLATE AND PROCESSES FOR PREPARATION THEREOF

(57) Abstract: The present invention provides novel polymorphs of lapatinib ditosylate, processes for preparing them, and pharmaceutical compositions comprising one or more of these polymorphs.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/043197

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/04 A61K31/517

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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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, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/02552 A1 (GLAXO GROUP LTD [GB]; MCCLURE MICHAEL SCOTT [US]; OSTERHOUT MARTIN HOW) 10 January 2002 (2002-01-10) cited in the application claims; figures; examples 9,10,15,18,24	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83
X	SACCHETTI MARK: "Determining the relative physical stability of anhydrous and hydrous crystal forms of GW2016." INTERNATIONAL JOURNAL OF PHARMACEUTICS 1 APR 2004, vol. 273, no. 1-2, 1 April 2004 (2004-04-01), pages 195-202, XP002538578 ISSN: 0378-5173 page 195 - page 196; figures; tables 1,2	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83

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

[X] See patent family 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	Date of mailing of the international search report
26 January 2010	02/02/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Härtinger, Stefan

Form PCT/ISA/210 (second sheet) (April 2005)

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 02/056912 A2 (GLAXO GROUP LTD [GB]; LACKEY KAREN ELIZABETH [US]; SPECTOR NEIL [US];) 25 July 2002 (2002-07-25) claims; example 1	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83
X	WO 2006/113649 A1 (SMITHKLINE BEECHAM CORK LTD [IE]; CARTER BARRY HOWARD [US]; CAMPBELL D) 26 October 2006 (2006-10-26) page 39; example 2 page 47 - page 48; claims	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83
X	WO 03/086467 A1 (SMITHKLINE BEECHAM CORP [US]; SPECTOR NEIL LEE [US]; XIA WENLE [US]) 23 October 2003 (2003-10-23) page 123 - page 124; example 1	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83
X	WO 2008/024439 A2 (CONCERT PHARMACEUTICALS INC [US]; TUNG ROGER [US]) 28 February 2008 (2008-02-28) page 38 - page 39; example 2	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83
A	BAI F ET AL: "Determination of lapatinib (GW572016) in human plasma by liquid chromatography electrospray tandem mass spectrometry (LC-ESI-MS/MS)" JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL SCIENCES & APPLICATIONS, ELSEVIER, AMSTERDAM, NL, vol. 831, no. 1-2, 2 February 2006 (2006-02-02), pages 169-175, XP025122816 ISSN: 1570-0232 [retrieved on 2006-02-02] page 172, right-hand column, last paragraph	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83
E	WO 2009/079541 A1 (SMITHKLINE BEECHAM CORK LTD [IE]; SMITHKLINE BEECHAM CORP [US]; CRAIG) 25 June 2009 (2009-06-25) page 23; claims; figures	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83

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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.
A	ANDERTON C: "A valuable technique for polymorph screening" EUROPEAN PHARMACEUTICAL REVIEW, vol. 9, no. 2, 2004, pages 68-74, XP002538579 page 68 - page 69	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83
A	CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS" TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954 page 164 - page 165	1-28, 31-37, 50-52, 62-65, 69-71, 73-74,83

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/043197

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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:

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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 fees, this Authority did not invite payment of additional fees.

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.:

1-28, 31-37, 50-52, 62-65, 69-71, 73-74, 83

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 and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-10, 83

   Form VI and process for preparing the same

1.1. claims: 11-21, 83

   Form XV and process for preparing the same

1.2. claims: 22-28, 83

   Form XIII and process for preparing the same

1.3. claims: 31-37, 83

   Form VIII and process for preparing the same

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2. claims: 29-30, 83

   Form XIX

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3. claims: 38-45, 83

   Form V

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4. claims: 46-49, 83

   Form XVIII

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5. claims: 50-52, 71, 83

   process for preparing Forms I and XII

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6. claims: 53-57, 83

   process for preparing Form II

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7. claims: 58-59, 83

   process for preparing Form III

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8. claims: 60-61, 83

   process for preparing Form IV

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. claims: 62-65, 83

process for preparing Form VIII

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10. claims: 66-68, 83

process for preparing Form IX

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11. claims: 69-70, 83

process for preparing Form XI

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12. claims: 72, 83

process for preparing Form XIV

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13. claims: 73-74, 83

process for preparing Forms XVI and XVII

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14. claims: 75-78, 83

process for preparing the monohydrate of lapatinib ditosylate

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15. claims: 79-83

process for preparing the anhydrous lapatinib ditosylate

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/043197

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0202552 A1	10-01-2002	AR 031248 A1	17-09-2003
		AT 353891 T	15-03-2007
		AU 7307101 A	14-01-2002
		AU 2001273071 B2	08-09-2005
		BR 0111947 A	06-05-2003
		CA 2413134 A1	10-01-2002
		CN 1440403 A	03-09-2003
		CN 1636992 A	13-07-2005
		CZ 20024223 A3	14-05-2003
		CZ 300945 B6	23-09-2009
		DE 60126611 T2	22-11-2007
		DK 1294715 T3	04-06-2007
		EP 1294715 A1	26-03-2003
		ES 2280382 T3	16-09-2007
		HK 1051041 A1	10-08-2007
		HU 0303022 A2	29-12-2003
		JP 4102185 B2	18-06-2008
		JP 2004502687 T	29-01-2004
		JP 2008050363 A	06-03-2008
		KR 20070100936 A	12-10-2007
		MX PA02012681 A	25-04-2003
		NO 20026196 A	24-02-2003
		NZ 522989 A	24-06-2005
		PL 365637 A1	10-01-2005
		PT 1294715 E	31-05-2007
WO 02056912 A2	25-07-2002	AT 290882 T	15-04-2005
		AU 2002236765 A1	30-07-2002
		DE 60203260 D1	21-04-2005
		DE 60203260 T2	02-02-2006
		EP 1353693 A2	22-10-2003
		ES 2236481 T3	16-07-2005
		JP 2004523522 T	05-08-2004
		US 2004053946 A1	18-03-2004
WO 2006113649 A1	26-10-2006	AR 054252 A1	13-06-2007
		AU 2006236423 A1	26-10-2006
		CA 2606207 A1	26-10-2006
		CN 101203211 A	18-06-2008
		EA 200702253 A1	28-04-2008
		EP 1871347 A1	02-01-2008
		JP 2008536931 T	11-09-2008
		KR 20080005557 A	14-01-2008
		US 2008206330 A1	28-08-2008
WO 03086467 A1	23-10-2003	AU 2003221684 A1	27-10-2003
WO 03086467 A1		EP 1492568 A1	05-01-2005
		JP 2005534623 T	17-11-2005
WO 2008024439 A2	28-02-2008	AU 2007288204 A1	28-02-2008
		CA 2661223 A1	28-02-2008
		CN 101594870 A	02-12-2009
		EP 2054063 A2	06-05-2009
		KR 20090042994 A	04-05-2009
		US 2008051422 A1	28-02-2008
WO 2009079541 A1	25-06-2009	NONE	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date