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(54) Title: THERAPY FOR COMPLICATIONS OF DIABETES

(57) Abstract: A selective ET_A receptor antagonist for use in a method for enhancing glycemic control and/or insulin sensitivity in a human subject having diabetic nephropathy and/or metabolic syndrome is disclosed. A selective ET_A receptor antagonist for use in treating a complex of comorbidities in an elderly diabetic human subject, wherein the selective ET_A receptor antagonist is for administration in combination or as adjunctive therapy with (a) at least one additional agent that is (i) other than a selective ET_A receptor antagonist and (ii) effective in treatment of diabetes and/or at least one of said comorbidities other than hypertension, and optionally (b) at least one antihypertensive other than a selective ET_A receptor antagonist is disclosed. Further, a therapeutic combination comprising a selective ET_A receptor antagonist and at least one antidiabetic, anti-obesity or antidiyslipidemic agent other than a selective ET_A receptor antagonist is disclosed.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/074013

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/505 A61P13/12

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, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOFMAN C ET AL: "Endothelin A antagonist LU-135252 and trandolapril in the treatment of the Cohen-Rosenthal diabetic hypertensive rat" BLOOD PRESSURE 2005 NO, vol. 14, no. 2, 2005, pages 114-119, XP009110942 ISSN: 0803-7051 1651-1999 the whole document ----- -/--	1-8, 10-28, 35-37, 50, 62-69, 71-89, 96-98

Further documents are listed in the continuation of Box C.

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.
- *G* document member of the same patent family

Date of the actual completion of the international search

20 January 2009

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15/04/2009

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/074013

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>FUKAMI K ET AL: "Novel therapeutic targets for diabetic nephropathy" ENDOCRINE, METABOLIC & IMMUNE DISORDERS - DRUG TARGETS, BENTHAM SCIENCE PUBLISHERS LTD, BUSSUM, NL, vol. 7, no. 2, 1 January 2007 (2007-01-01), pages 83-92, XP009110527 ISSN: 1871-5303 page 87, left-hand column, last paragraph - right-hand column, paragraph F</p>	<p>1-8, 10-28, 35-37, 50, 62-69, 71-89, 96-98</p>
X	<p>HOCHER B ET AL: "Effects of endothelin receptor antagonists on the progression of diabetic nephropathy" NEPHRON,, vol. 87, no. 2, 1 February 2001 (2001-02-01), pages 161-169, XP009110722 ISSN: 0028-2766 the whole document</p>	<p>1-8, 10-28, 35-37, 50, 62-69, 71-89, 96-98</p>
X	<p>EP 0 647 449 A (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 12 April 1995 (1995-04-12)</p> <p>claims 1,18-21</p>	<p>1-8, 10-28, 35-37, 50, 62-69, 71-89, 96-98</p>
X	<p>DHEIN S ET AL: "Long-term effects of the endothelin(A) receptor antagonist LU 135252 and the angiotensin-converting enzyme inhibitor trandolapril on diabetic angiopathy and nephropathy in a chronic type I diabetes mellitus rat model." THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS MAY 2000, vol. 293, no. 2, May 2000 (2000-05), pages 351-359, XP002511102 ISSN: 0022-3565 the whole document</p>	<p>1-8, 10-28, 35-37, 50, 62-69, 71-89, 96-98</p>
X	<p>WENZEL ET AL: "SPP301 Phase IIb Results in Diabetic Nephropathy Presented at ASN" INTERNET, [Online] 12 November 2005 (2005-11-12), XP002511103 Retrieved from the Internet: URL:http://www.redorbit.com/news/health/303255/spp301_phase_iib_results_in_diabetic_nephropathy_presented_at_asn/index.html?source=r_health> [retrieved on 2009-01-14] the whole document</p>	<p>1-8, 10-28, 35-37, 50, 62-69, 71-89, 96-98</p>
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/074013

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BALSIGER BRUNO ET AL: "Endothelin A-receptor blockade in experimental diabetes improves glucose balance and gastrointestinal function" CLINICAL SCIENCE (LONDON), vol. 103, no. Suppl. 48, August 2002 (2002-08), pages 430S-433S, XP002511104 ISSN: 0143-5221 page 4321, left-hand column, paragraph 2 page 432S, right-hand column, paragraph DISCUSSION - page 433S -----</p>	<p>1-8, 10-28, 35-37, 50, 62-69, 71-89, 96-98</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/074013

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 allsearchable 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.:
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.:

1 (in part)-3(in part), 4-8, 10(in part)-28(in part), 35(in part)

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(in part)-3(in part), 4-8, 10(in part)-28(in part), 35(in part)-37(in part), 50(in part), 62-64 (in part), 65-69, 71(in part)-89(in part), 96(in part)-98(in part)

The claims are directed to a selective ETA receptor antagonist for use in the treatment of diabetic nephropathy.

2. claims: 1(in part)-3(in part), 9, 10(in part)-28(in part), 29-34, 35(in part)-37(in part), 50(in part), 62-64 (in part), 70, 71(in part)-89(in part), 90-95, 96(in part)-98(in part)

The claims are directed to a selective ETA receptor antagonist for use in the treatment of metabolic syndrome.

3. claims: 38-49, 51, 99-110

The claims are directed to a selective ETA receptor antagonist in combination with an additional active agent for use in the treatment of a complex of comorbidities in an elderly diabetic subject.

4. claims: 52-61

The claims are directed to a therapeutic combination comprising a selective ETA receptor antagonist in combination with an antidiabetic, anti-obesity or antidyslipidemic agent.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/074013

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0647449	A	12-04-1995	CA	2126619 A1	25-12-1994
			CN	1109780 A	11-10-1995
			FI	943071 A	25-12-1994
			NO	942396 A	27-12-1994
