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(54) Title: COMBINED USE OF A GLP-1 COMPOUND AND A MODULATOR OF DIABETIC LATE COMPLICATIONS

(57) Abstract: Methods and uses for treatment of diabetic late complications comprising administration of a GLP-1 compound and a modulator of diabetic complications.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00888

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K38/26 A61K31/35 //A61P3/10				
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 A61P C07D				
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, MEDLINE, WPI Data, EMBASE, 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	EP 1 088 824 A (PFIZER PROD INC) 4 April 2001 (2001-04-04) page 11, line 19 - line 20 page 18, line 26 - line 27 page 19, line 18 - line 46 abstract; claims 14,15 ---	1-6, 18-32, 44-52		
X	EP 1 092 711 A (TAKEDA CHEMICAL INDUSTRIES LTD) 18 April 2001 (2001-04-18) page 36, line 18 - line 19 page 36, line 38 - line 56 page 37, line 3 - line 5 --- -/--	1-6, 19-32, 35-52		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</td> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> Patent family members are listed in annex.</td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.	<input checked="" type="checkbox"/> Patent family members are listed in annex.
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.	<input checked="" type="checkbox"/> 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	"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			
"E" earlier document but published on or after the international filing date	"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			
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"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family			
"P" document published prior to the international filing date but later than the priority date claimed				
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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 <h2 style="text-align: center;">Yvonne Siösteen</h2>			

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 02/00888

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 01 66135 A (NOVO NORDISK AS) 13 September 2001 (2001-09-13) page 8, line 12 - line 21 page 11, line 34 -page 12, line 5 ---	9-30, 35-52
A	US 5 447 946 A (KURONO MASAYASU ET AL) 5 September 1995 (1995-09-05) the whole document ---	5,6,31, 32
A	DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; August 2001 (2001-08) TOFT-NIELSEN M B ET AL: "Determinants of the effectiveness of glucagon-like peptide-1 in type 2 diabetes." Database accession no. NLM11502823 XP002902901 abstract & THE JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM. UNITED STATES AUG 2001, vol. 86, no. 8, August 2001 (2001-08), pages 3853-3860, ISSN: 0021-972X -----	1-52

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00888

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.: **1-26**
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. Claims Nos.: **1-52 (partially)**
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:

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 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

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

1. Claims: 31,32, 5, 6 and part of claims 27-30, 44-52, 1-4,
18-26

Claims 31,32, 5, 6 and part of claims 27-30, 44-52, 1-4, 18-26 directed to the use of a GLP-1 compound and an aldose reductase inhibitor for the preparation of a medicament for the treatment of diabetic late complications.

2. Claims: 33,34,7, 8 and part of claims 27-30, 44-52,18-26

Claims 33,34, 7, 8 and part of claims 27-30, 44-52, 18-26 directed to the use of a GLP-1 compound and an protein kinase C inhibitor for the preparation of a medicament for the treatment of diabetic late complications.

3. Claims: 35-43, 9-17 and part of the claims 27-30, 44-52,
18-26

Claims 35-43, 9-17 and part of claims 27-30, 44-52, 18-26 directed to the use of a GLP-1 compound and an antihypertensive agent for the preparation of a medicament for the treatment of diabetic late complications.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 1-26

Claim 1-26 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body (Rule 39.1 (iv)). Nevertheless, a search has been executed for claims 1-26, partly. The search has been based on the alleged effects of the compounds/compositions.

Continuation of Box I.2

Claims Nos.: 1-52 (partially)

The present application relates to the use of GLP-1 in combination with a compound chosen from a large number of possible compounds. These compounds are defined by reference to a desirable characteristic or property, namely the ability to be used as a modulator of a diabetic late complication. Support within the meaning of Article 6 PCT and/or 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.

Present claims 31, 5, 18-26 relate to a compound defined by reference to a desirable characteristic or property, an aldose reductase inhibitor. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only the compound fidarestat ("fidarest" has been interpreted as fidarestat). Additionally, previously known compounds may be included in the scope of the present claims. 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.

Expressions such as "protein kinase C inhibitor", "antihypertensive agent", "angiotensin converting enzyme inhibitor", "angiotensin II receptor antagonist" and "non-subtype selective beta-adrenergic antagonist" are also unclear.

The claims also relate to treatment of diseases which are not well defined. The use of the definition "diabetic late complication" in the present context is considered to lead to lack of clarity of Article 6 PCT. It is not fully possible to determine the diseases for which protection is being sought. The lack of clarity is such as to render a meaningful complete search not fully possible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

related to the use of the aldose reductase inhibitor fidarestat in combination with a GLP-1 compound for the preparation of a medicament for treating the diabetic complications: diabetic hypertension, nephropathy, neuropathy and retinopathy.

The search has also been directed to compounds described as being aldose reductase inhibitors, antihypertensive agents etc.

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/DK 02/00888

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