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(54) Title: C1-INH COMPOSITIONS AND METHODS FOR THE PREVENTION AND TREATMENT OF DISORDERS ASSOCIATED WITH C1 ESTERASE INHIBITOR DEFICIENCY

(57) Abstract: Compositions and methods for the treatment and/or prevention of disorders associated with C1 esterase inhibitor deficiency are disclosed.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/30309

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 38/00, A61P 5/00, A61P 31/00, A61K 38/48, A61K 38/55, C07K 14/81, A61K 38/16 (2014.01)
 CPC - A61K 38/00, C07K 14/47, C07K 2319/00, A01K 2217/05, A61K 38/1709, A61K 38/10
 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)
 CPC- A61K 38/00, C07K 14/47, C07K 2319/00, A01K 2217/05, A61K 38/1709, A 61K38/10
 IPC(8)- A61K 38/00, A61P 5/00, A61P 31/00, A61K 38/48, A61K 38/55, C07K 14/81, A61K 38/16 (2014.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 IPC(8)- A61P 35/00, C07K 14/515 (2014.01) USPC- 514/20.1, 514/21.2, 514/13.3, 514/15.4, 514/16.4, 514/16.6, 530/380, 530/395, 530/351
 CPC- A61K 38/16, A61K 38/177, A01N 63/02, C07K 7/08, A61K 38/1751, C07D 211/60, C07D 307/14, C07D 307/52

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PubWEST (PGPB, USPT, USOC, EPAB, JPAB); PatBase, Google/Scholar: complement component 1 inhibitor, C1NH; HAE1; HAE2; C1INH; C1-INH; Plasma protease C1 inhibitor; serine/cysteine proteinase inhibitor clade G member 1, C1 esterase inhibitor, C1 inhibitor, U/ml; activity, Serping1, benzoyl arginine ethyl ester, Cinryze, ViroPharma Incorporated, Cynthia Gallag

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,090,777 A (Hack, et al.) 18 July 2000 (18.07.2000) claim 1; col 7, ln 10-35; col 8, ln 50-65; col 9, ln 40 to col 10, ln 10; col 10, ln 65 to col 11, ln 10;	1-9
Y	Schreiber, et al. Inhibition by CalNH of Hageman Factor Fragment Activation of Coagulation, Fibrinolysis, and Kinin Generation. J Clin Invest. 1973, 52(6):1402-1409; pg 1404, Fig 2, 3 and their legends; pg 1405, col 1	1-9

Further documents are listed in the continuation of Box C.

* 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 application or patent 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
"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)	"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
"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	

Date of the actual completion of the international search 06 October 2014 (06.10.2014)	Date of mailing of the international search report 07 NOV 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/30309

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:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I: claims 1-9, drawn to a method for treating, inhibiting, or preventing a disorder associated with a deficiency in C1 esterase inhibitor in a subject in need thereof, said method comprising administering a composition comprising at least one C1 esterase inhibitor, wherein said C1 esterase inhibitor is present at about 400 U/ml or more.

Group II: claim 10-15, drawn to a composition comprising at least one C1 esterase inhibitor at about 400 U/ml or more.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

***** See Supplemental Sheet to continue *****

- 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 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.:
1-9

- 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.

***** Supplemental Sheet *****

In Continuation of Box III. Observations where unity of invention is lacking:

Special Technical Features

The inventions of Group II do not include the shared or common technical feature of a method comprising administering a composition comprising at least one C1 esterase inhibitor, wherein said C1 esterase inhibitor is present at about 400 U/ml or more, as required by Group I.

Common Technical Features

The inventions of Groups I-II share the technical feature of a composition comprising at least one C1 esterase inhibitor at about 400 U/ml or more. However, this shared technical feature does not represent a contribution over prior art as being anticipated by a paper titled "Inhibition by C1INH of Hageman Factor Fragment Activation of Coagulation, Fibrinolysis, and Kinin Generation" by Schreiber, et al. (J Clin Invest. 1973; 52(6):1402-1409) (hereinafter "Schreiber") that discloses a composition comprising at least one C1 esterase inhibitor at about 400 U/ml or more (pg 1405, col 1, "fractions containing C1INH eluted at 55% of bed volume and were pooled (total volume 27 ml) and stored at -70C... This highly purified C1INH preparation (6,000 U/ml) gave a double band on alkaline disc gel electrophoresis in a region from which unstained gels yielded active C1INH upon elution (Fig. 4)", wherein C1INH is synonymous with C1 esterase inhibitor, as evidenced by a paper titled "Angioedema due to acquired C1-esterase inhibitor deficiency in a patient with Helicobacter pylori infection" by Farkas, et al. (Z Gastroenterol. 1999, 37(6):513-8) (Abstract, "The first component of the classical pathway of the complement system, C1 is regulated by a serum protein, the C1-esterase inhibitor (C1-INH)"). As said technical feature was known in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the groups.

Groups I-II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note regarding claim 10:

Claim 10 is objected to as unclear, because it is drawn to a composition comprising C1 esterase, while the specification discloses a composition comprising C1 esterase inhibitor (please see instant application, pg 5, ln 7-15, "Compositions comprising at least one C1 esterase inhibitor and, optionally, at least one pharmaceutically acceptable carrier (e.g., one suitable for subcutaneous or intravenous administration) are encompassed by the instant 10 invention. Such compositions may be administered, in a therapeutically effective amount, to a patient in need thereof for the treatment of a disorder associated with C1 esterase inhibitor deficiency. The instant invention also encompasses kits comprising at least one composition of the instant invention, e.g., a composition comprising at least one C1 esterase inhibitor"). For the purpose of this Lack of Unity argument, this ISA/USA construed claim 10 as being drawn to a composition comprising C1 esterase inhibitor as follows:

10. A composition comprising at least one C1 esterase inhibitor at about 400 U/ml or more.