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(54) Title: METHODS OF TREATMENT WITH GLP-1 RECEPTOR AGONISTS

(57) Abstract: The invention provides methods for treating diabetes or obesity, as well as methods for inducing weight loss, preventing weight gain, or controlling weight in a patient in need thereof. The methods comprise administering to the patient at least one effective dose of a GLP-1 receptor agonist, or a regimen of GLP-1 receptor agonist comprising a plurality of substantially evenly spaced doses. The effective dose or regimen does not induce substantial nausea or appetite suppression in the patient.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/44383

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/26; A61P 3/04, A61P 3/10, A61P 7/12; C07K 14/605 (2012.01)

USPC - 514/4.8, 514/6.9, 514/7.2, 514/7.3, 514/11.7

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)

USPC: 514/4.8, 514/6.9, 514/7.2, 514/7.3, 514/11.7

IPC(8): A61K 38/26; A61P 3/04, A61P 3/10, A61P 7/12; C07K 14/605 (2012.01)

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 practicable, search terms used)

PubWEST (DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ), Google Scholar, Google Patents, PatBase

Search Terms Used: weight, GLP-1, receptor, agonist, nausea, GLP-1 7-36, appetite, suppression, satiety, anorexia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/053946 A1 (Brindon et al.) 18 May 2007 (18.05.2007) esp: para [0012], [0018], [0042] -[0045], [0053], [0056], [0103], [0103], [0010], [0011], [0052], [00176], [0054], [0055], [0059], [0038], [00157], [00161].	1-4
Y	US 6,191,102 B1 (DiMarchi et al.) 20 February 2001 (20.02.2001) entire document.	1-4
Y	US 5,846,937 A (Drucker) 08 December 1998 (08.12.1998) entire document.	1-4
Y	US 2010/0009904 A1 (Lv et al.) 14 January 2010 (14.01.2010) entire document.	1-4
Y	US 2010/0144621 A1 (Kim et al.) 10 June 2010 (10.06.2010) entire document.	1-4
Y	US 2009/0186818 A1 (Lundemose) 23 July 2009 (23.07.2009) entire document.	1-4

☐ 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

"E" earlier application or patent 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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/44383

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.: 5-71, 90-100 and 108-109
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. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

---continued on first extra page---

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.:
1-4

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.

Continuation of Box III Lack of Unity of Invention:

Group I: Claims 1-4, drawn to A method of inducing weight loss in a patient in need thereof, comprising administering at least one effective dose of a GLP-1 receptor agonist, wherein the effective dose does not induce substantial appetite suppression in the patient; AND A method of preventing weight gain in a patient in need thereof, comprising administering at least one effective dose of a GLP-1 receptor agonist, wherein the effective dose does not induce substantial appetite suppression in the patient; AND A method of controlling weight in a patient in need thereof, comprising: administering a GLP-1 receptor agonist regimen to the patient, the regimen being effective to maintain therapeutic serum levels of said GLP-1 receptor agonist below a nausea-inducing threshold level, and/or avoid a nausea-inducing rise in GLP-1 levels.

Group II: Claims 72-89, drawn to a method for treating diabetes in a patient in need thereof, without inducing substantial nausea, comprising: administering a regimen of GLP-1 receptor agonist formulated for sustained release and slow uptake to the patient's circulation when administered.

Group III: Claims 101-107, drawn to a method for treating type 1 or type 2 diabetes or obesity in a patient in need thereof, comprising: administering once weekly a GLP-1-ELP fusion protein exhibiting slow uptake from an injection site, and at a dose equivalent to about 50 mg to about 100 mg of SEQ ID NO: 13; AND A unit dose of a GLP-1-ELP fusion protein, the unit dose having from 50 mg to 100 mg of the fusion formulated for subcutaneous injection.

The inventions listed as Groups I-III 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:

Groups I-II do not include the inventive concept of administering once weekly a GLP-1-ELP fusion protein exhibiting slow uptake from an injection site, and at a dose equivalent to about 50 mg to about 100 mg of SEQ ID NO: 13; or A unit dose of a GLP-1-ELP fusion protein, the unit dose having from 50 mg to 100 mg of the fusion formulated for subcutaneous injection, as required by Group III.

Group I does not include the inventive concept of a method for treating diabetes in a patient in need thereof, comprising: administering a regimen of GLP-1 receptor agonist formulated for sustained release and slow uptake to the patient's circulation when administered, as required by Group II.

Group III does not include the inventive concept of a method for treating diabetes in a patient in need thereof, without inducing substantial nausea, comprising: administering a regimen of GLP-1 receptor agonist formulated for sustained release, as required by Group II.

Group II does not include the inventive concept of a method of inducing weight loss /preventing weight gain in a patient in need thereof, comprising administering at least one effective dose of a GLP-1 receptor agonist, wherein the effective dose does not induce substantial appetite suppression in the patient, as required by Group I.

Group III does not include the inventive concept that wherein the effective dose does not induce substantial appetite suppression in the patient, or that the regimen being effective to maintain therapeutic serum levels of said GLP-1 receptor agonist below a nausea-inducing threshold level, and/or avoid a nausea-inducing rise in GLP-1 levels, as required by Group I.

Groups I-II share the technical feature of a method for treating a metabolic disorder in a patient in need thereof, without inducing substantial nausea, comprising: administering a GLP-1 receptor agonist regimen to the patient.

Groups I-III share the technical feature of a method for treating obesity/controlling weight in a patient in need thereof, comprising administering a GLP-1 receptor agonist to the patient at a specific dose.

Groups II-III share the technical feature of a method for treating diabetes in a patient in need thereof, comprising: administering a GLP-1 receptor agonist formulated for slow uptake when administered.

However, these shared technical features do not represent a contribution over the prior art, specifically, WO 2007/053946 A1 to Bridon et al. (hereinafter 'Brion') teaches a method for controlling weight and/or treating diabetes or obesity in a patient in need thereof (para [0012]-the methods of the invention comprise the step of administering to the subject an amount of conjugated insulinotropic peptide effective for treating a disorder or condition while providing reduced nausea side effect. Exemplary conditions or disorders treatable with insulinotropic peptides include, but are not limited to, obesity and diabetes, including maturity onset diabetes mellitus (type II diabetes)', [0053], [0056]), comprising:

--administering a dose of GLP-1 receptor agonist (para [0012], [0095]-'Useful insulinotropic peptides include GLP-1, exendin-3 and exendin-4, and their precursors, derivatives and fragments', [0102]-[0103]-'Useful peptides for the methods described herein include those which are derivable from GLP-1 such as GLP-1(1-37) and GLP-1(7-36)') regimen to the patient (para [0010]-[0012], [0052], [0053]),

--the regimen being effective to avoid nausea when administered (table 1; para [0054]-[0059]-'that the methods of the invention encompass the prevention, reduction, and elimination of nausea in a subject receiving an insulinotropic peptide for the treatment of a disorder or condition by selecting patients who are prone to experiencing, have experienced, or are experiencing nausea', [00176], [0091]-'Similarly, amounts sufficient to prevent, manage, treat or ameliorate such disorders or conditions, but still sufficient to reduce nausea relative to administration of an unconjugated insulinotropic peptide are also encompassed by the above described dosage amounts and dose frequency schedules'); and/or

--the regimen of GLP-1 receptor agonist being formulated for slow uptake to the patient's circulation when administered (para [00176]-'The pharmacokinetic profile exhibited slow absorption and a prolonged exposure, with plasma drug levels rising for 4 to 6 days and then declining thereafter');

--wherein said GLP-1 receptor agonist could be administered by injection (para [00178]).

As said shared technical features were known at the time of the invention, these cannot be considered special technical feature that would otherwise unify the groups.

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