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(54) Title: PROCESSES FOR THE PREPARATION OF OCTREOTIDE

(57) Abstract: The invention relates to processes for the preparation of pure octreotide or pharmaceutically acceptable salts thereof. The invention also relates to an amorphous form of octreotide and processes for the preparation of amorphous form of octreotide or pharmaceutically acceptable salts thereof. The invention also relates to pharmaceutical compositions that include the pure octreotide or the amorphous octreotide or pharmaceutically acceptable salts thereof.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB07/00800

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 38/04(2006.01);C07K 16/00(2006.01)

USPC: 530/328,317,333;424/177.1

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)
U.S. : 530/328, 317, 333; 424/177.1

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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,987,167 B2 (CHATURVEDI et al) 17 January 2006 (17.01.2006), the whole document.	1-5, 11 and 13
A	US 4,395,403 A (BAUER et al) 26 July 1983 (26.07.1983), the whole document.	1-5, 11 and 13

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	"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 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

20 June 2008 (20.06.2008)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB07/00800

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:
Please See Continuation 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 additional fees, this Authority did not invite payment of any 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.: 1-5,11 and 13

- 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.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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.

Group I, claim(s) 1-5, 11 and 13, drawn to a process for the preparation of R_1 -(D)Phe-Cys(Acm)-Phe-OH.

Group II, claim(s) 6 and 7, drawn to a process for the preparation of L-Thr-Ome.

Group III, claim(s) 8-10, drawn to a process for removal of inorganic impurities from R_1 -Cys(Acm)-Thr-OL.

Group IV, claim(s) 14-19, drawn to a process for the preparation of trifluoroacetate salt of 8P-OL and product thereof.

Group V, claim(s) 20, 21 and 23, drawn to a process for the preparation of octreotide or a salt thereof and product thereof.

Group VI, claim(s) 22 and 24-31, drawn to a process for the preparation of octreotide acetate by preparative chromatography and product thereof.

The inventions listed as Groups I-VI 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: The processes of Groups I-VI each has different scope. They do not have common technical features that are inventive. That what is common is known, and if known is not special. For example, preparation of octreotide is known in the art as acknowledged on page 2, line 1 in the instant disclosure (See e.g., U.S. Patent No. 4,395,403). Similarly, page 4, lines 2 and 26 of the instant disclosure teach that the intermediates recited in the claims can be converted to octreotide or salts thereof by process known in the art. Further, there are no special features linking the process and the product. Therefore, since the groups do not share the same special technical features, the invention do not relate to a single inventive concept.

Continuation of B. FIELDS SEARCHED Item 3:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB07/00800

APS, CAS ONLINE, REGISTRY, DIALOG, MEDLINE, EMBASE, BIOSIS, WPIDS

search terms: amino acids, peptides, proteins, prepar? mak? synthes?, produc? cyclic octapeptide octreotide, react? or reagent? L-phenylalanine, N-[(1,1-dimethylethoxy) carbonyl]-D-phenylalanine-S-[(acetylamino)methyl]-L-cysteinyl-, methyl ester, 2, 2, 2-trifluoroacetate.