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(71) Applicant (for all designated States except US): **NEKTAR THERAPEUTICS AL, CORPORATION** [US/US]; 490 Discovery Drive, Huntsville, AL 35806 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BOSSARD, Mary, J.** [US/US]; 120 Kelvingrove Drive, Madison, AL 35758 (US).

(74) Agents: **WILSON, Mark, A.** et al.; Nektar Therapeutics, 150 Industrial Road, San Carlos, CA 94070 (US).

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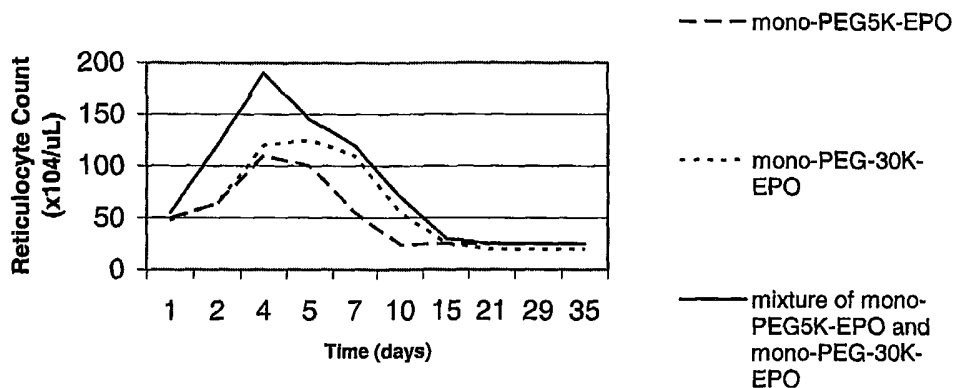
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(54) Title: COMPOSITIONS COMPRISING TWO DIFFERENT POPULATIONS OF POLYMER-ACTIVE AGENT CONJUGATES

Time Course of Reticulocyte Counts



(57) Abstract: Compositions comprising two different populations of polymer-active agent conjugates, wherein the weight average molecular weight of the polymers associated with each population is different, are provided. Also provided are methods preparing such compositions and methods for administering such compositions.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/041328

A. CLASSIFICATION OF SUBJECT MATTER

A61K47/48

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, WPI Data, PAJ, BIOSIS, 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	WO 96/17626 A (RYAN PHARMACEUTICALS, INC; UNIVERSITY OF WASHINGTON; NATIONAL RESEARCH) 13 June 1996 (1996-06-13) page 15, lines 22-25; claims 13-16; examples 10,11,13,14	1-22, 28-30, 33,40-58
X	BOWEN S. ET AL: "Relationship between molecular mass and duration of activity of polyethylene glycol conjugated granulocyte colony-stimulating factor mutein" EXPERIMENTAL HEMATOLOGY, vol. 27, 1999, pages 425-432, XP008053962 page 429, column 1; figures 1,5-7	1-3,8,9, 15-22, 28-30, 33,39-58
Y	EP 1 333 036 A (CHUGAI SEIYAKU KABUSHIKI KAISHA) 6 August 2003 (2003-08-06) cited in the application figures 12-14; examples 8,9,11	1-36, 39-58
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☒ Further documents are listed in the continuation of box C.

☒ 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

"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

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"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

18 October 2005

Date of mailing of the international search report

-2. 02. 2006

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

Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YAMAOKA ET AL: "Distribution and Tissue Uptake of Poly(ethylene glycol) with Different Molecular Weights after Intravenous Administration to Mice" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 83, no. 4, April 1994 (1994-04), pages 601-606, XP002062331 ISSN: 0022-3549 abstract page 605, column 2, paragraph 2 -----	1-36, 39-58
Y	BAILON P. ET AL: "Polyethylene glycol-conjugates pharmaceutical proteins" PSTT, vol. 1, 1998, pages 352-356, XP002349366 page 352, column 2, paragraph 3; figure 1 -----	1-36, 39-58
A	ROBERTS M. J. ET AL: "Chemistry for peptide and protein PEGylation" ADVANCED DRUG DELIVERY REVIEWS, vol. 54, 2002, pages 459-476, XP002349367 abstract; figure 14 page 473 -----	1-36, 39-58
A	WO 01/02017 A (F. HOFFMANN-LA ROCHE AG) 11 January 2001 (2001-01-11) abstract -----	1-36, 39-58
E	WO 2005/000360 A (NEKTAR THERAPEUTICS AL, CORPORATION; HARRIS, J., MILTON; KOZLOWSKI, AN) 6 January 2005 (2005-01-06) page 16 page 53, paragraph 3 - page 54, paragraph 1 page 59, paragraph 3 page 67, paragraph 1 page 69, paragraph 3 -----	1-3, 8-10,13, 17,18, 21-30, 33-36, 39-57

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/041328

Box 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:
Although claims 53-58 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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 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.:
1-36, 39-58 (all partially)

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: 1-36,39-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (alkylene oxide) and where the active agent is a protein, preferably erythropoietin. Method for its preparation and use for the delivery of the composition to a patient.
Excluding the subject matter of inventions 2-18.

2. claims: 1-21,28-31,34-36,39-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly(vinyl pyrrolidone) and where the active agent is a protein, preferably erythropoietin. Method for its preparation and use for the delivery of the composition to a patient.
Excluding the subject matter of inventions 1, 3-18.

3. claims: 1-21,28-31,34-36,39-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (vinyl alcohol) and where the active agent is a protein, preferably erythropoietin. Method for its preparation and use for the delivery of the composition to a patient.
Excluding the subject matter of inventions 1, 2, 4-18.

4. claims: 1-21,28-31,34-36,39-58 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a polyoxazoline and where the active agent is a protein, preferably erythropoietin. Method for its preparation and use for the delivery of the composition to a patient.
Excluding the subject matter of inventions 1-3, 5-18.

5. claims: 1-21,28-31,34-36,39-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (acryloylmorpholine) and where the active agent is a protein, preferably erythropoietin. Method for its preparation and use for the delivery of the composition to a patient.
Excluding the subject matter of inventions 1-4, 6-18.

6. claims: 1-21,28-31,34-36,39-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (oxyethylated polyol) and where the active agent is a protein, preferably erythropoietin. Method for its preparation and use for the delivery of the composition to a patient.
Excluding the subject matter of inventions 1-5, 7-18.

7. claims: 1-33,37,40-58 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (alkylene oxide) and where the active agent is a small molecule. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-6, 8-18.

8. claims: 1-21,28-31,37,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (vinyl pyrrolidone) and where the active agent is a small molecule. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-7, 9-18.

9. claims: 1-21,28-31,37,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (vinyl alcohol) and where the active agent is a small molecule. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-8, 10-18.

10. claims: 1-21,28-31,37,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a polyoxazoline and where the active agent is a small molecule. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-9, 11-18.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

11. claims: 1-21,28-31,37,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (acryloylmorpholine) and where the active agent is a small molecule. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-10, 12-18.

12. claims: 1-21,28-31,37,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (oxyethylated polyol) and where the active agent is a small molecule. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-11, 13-18.

13. claims: 1-33,38,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (alkylene oxide) and where the active agent is a peptide. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-12, 14-18.

14. claims: 1-21,28-31,38,40-58 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (vinyl pyrrolidone) and where the active agent is a peptide. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-13, 15-18.

15. claims: 1-21,28-31,38,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (vinyl alcohol) and where the active agent is a peptide. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-14, 16-18.

16. claims: 1-21,28-31,38,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a polyoxazoline and where the active agent is a peptide. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-15, 17,18.

17. claims: 1-21,28-31,38,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (acryloylmorpholine) and where the active agent is a peptide. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-16, 18.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

18. claims: 1-21,28-31,38,40-58 in part

A composition comprising a first population of polymer-active agent conjugates and a second population of polymer-active agent conjugates wherein the weight average molecular weight of the one or more polymers in the first population is different from the weight average molecular weight of the one or more polymers in the second population, and where the polymer is a poly (oxyethylated polyol) and where the active agent is a peptide. Method for its preparation and use for the delivery of the composition to a patient.

Excluding the subject matter of inventions 1-17.

INTERNATIONAL SEARCH REPORT

International Application No
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