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CARLOS R. OLARTE, mayor y vecino de Bogotá. D.C., identificado como aparece al pie de mi firma, actuando en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad en el doctor **ALVARO CORREA ORDOÑEZ**, identificado con la Cédula de Ciudadanía número 79.143.366 de Usaquén y con la Tarjeta Profesional número 20.281, para que sea él quien en adelante, asuma el trámite de la presente solicitud.

El apoderado sustituto queda con las mismas facultades del principal.

Atentamente,



CARLOS R OLARTE

C.C. No. 79.782.747 de Bogotá

T. P. No. 74.295 del Consejo Superior de la Judicatura

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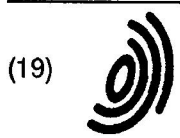
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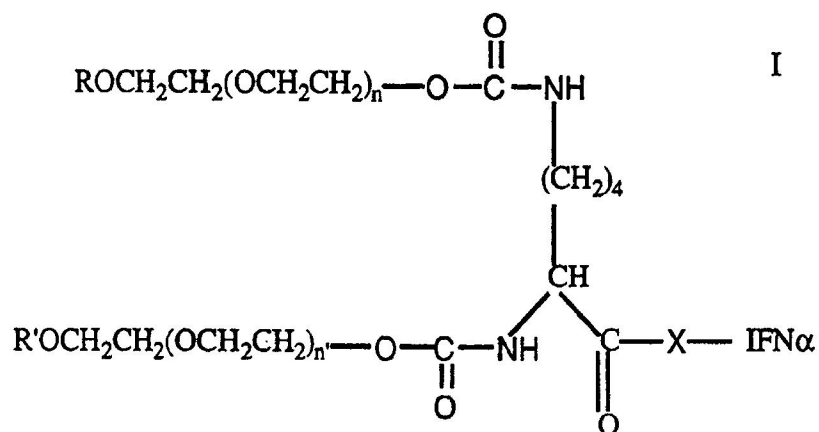
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(54) Interferon conjugates

(57) Physiologically active PEG-IFN α conjugates having a formula as follows:

Description

Interferon, in particular interferon α 2a, is a pharmaceutically active protein which has antiviral and antiproliferative activity. For example interferon is used to treat hairy cell leukemia and Kaposi's sarcoma, and is active against hepatitis. In order to improve stability and solubility, and reduce immunogenicity, pharmaceutically active proteins such as interferon may be conjugated to the polymer polyethylene glycol (PEG).

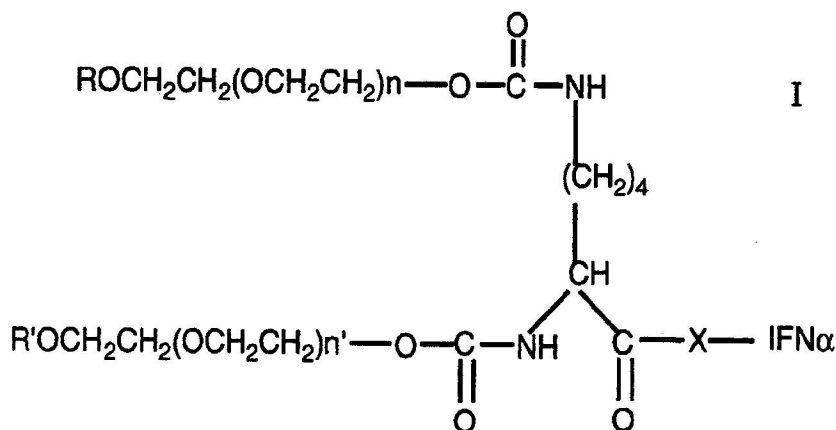
The bioavailability of protein therapeutics are often limited due to their short plasma half-life, thus preventing them from attaining their maximum clinical potency. In recent years, PEG conjugated biomolecules have been shown to possess clinically useful properties (Inada et al., J. Bioact. and Compatible Polymers 5, 343 (1990); Delgado et al., Critical Reviews in Therapeutic Drug Carrier Systems 9, 249 (1992); Katre, Advanced Drug Delivery Systems 10, 91 (1993)). Among these are better physical and thermal stability, protection against susceptibility to enzymatic degradation, increased solubility, longer *in vivo* circulating half-life, decreased clearance and enhancing potency. It has been reported that branched PEG conjugates exhibit increased pH and thermal stability and greater stability towards proteolytic digestion than linear PEG conjugates. (Monfardini et al., Bioconjugate Chem. 6, 62 (1995)). Other properties of PEG proteins are reduced immunogenicity and antigenicity, as well as reduced toxicity. Another effect of PEGylation of certain proteins may be reduced *in vitro* activity accompanied by enhanced *in vivo* activity. This has been observed in G-CSF (Satake-Ishikawa et al., Cell Structure and Function 17, 157-160 (1992)), IL-2 (Katre et al., Proc. Natl. Acad. Sci. USA 84, 1487 (1987)), TNF- α (Tsutsumi et al., Jpn. J. Cancer Res. 85, 9 (1994)), IL-6 (Inoue et al., J. Lab. Clin. Med. 124, 529 (1994)) and CD4-IgG (Chamow et al., Bioconj. Chem. 5, 133 (1994)), among others.

It has been now observed that in the case of interferon, PEGylation reduces *in vitro* antiviral activity but increases antiproliferative activity in human tumor cells. However the new PEG interferon conjugate of this invention has surprising properties in that the antiproliferative activity of the PEG interferon is much higher than that not only of interferon but of other PEG interferon conjugates. Although the antiproliferative activity of the conjugate is much increased over other PEG interferon- α conjugates, yet the reduction in antiviral activity is similar. In addition, the PEG interferon- α conjugate of this invention is non-immunogenic, it elicits virtually no antibody formation. In contrast, other PEG interferon- α conjugates do elicit limited antibody formation.

Accordingly, the invention is a new class of PEG derivatives of interferon α (IFN α). The conjugate of this invention has a branched PEG structure, as can be seen below. The branched PEG has the advantage of allowing the attachment of 2 linear PEG molecules at a single site, thus doubling the attached PEG mass without multiple sites of PEGylation.

Compared to unmodified IFN α (i.e. IFN α without a PEG attached), the conjugate has an increased circulating half-life and plasma residence time, reduced immunogenicity, decreased clearance, and increased antiproliferative activity, concomitant with decreased *in vitro* antiviral activity. Compared with other PEG-IFN α conjugates, the conjugate of this invention has a much greater antiproliferative activity, disproportionate to the enhancement or reduction that occurs in its other characteristics, and virtually no immunogenicity.

The physiologically active PEG-IFN α conjugate species of this invention has the formula:



The conjugate of this invention has the same uses as IFN α , for example, antiproliferative uses. In particular, the PEG interferon- α conjugates of this invention are useful to treat immunomodulatory disorders such as neoplastic diseases, for example, hairy cell leukemia, CML, and Kaposi's sarcoma, and infectious diseases, in the same way IFN α s (especially IFN α 2a) are used to treat these diseases. However, the conjugate of this invention has improved properties including superior stability, greater solubility, enhanced circulating half-life and plasma residence times. In addition,

Table 4

Immunogenicity		
Treatment	Antibody (INU/ml) *	
	Median	Range
IFN α 2a	2,400	217-8,533
IFN α 2a Aggregates	42,667	8,000-768,000
Conjugate of Formula I	0	0-1,133

* Interferon neutralizing units/ml

Example 6

Antitumor activity *In Vivo*

The *in vivo* antitumor activity of a conjugate of Formula I (PEG2-IFN α 2a) and unmodified IFN α 2a were evaluated by determining their ability to reduce the size of various human tumor cells implanted subcutaneously into mice. Results are shown in Figures 1-6.

Procedure: Athymic nude mice (Harlan) received a subcutaneous implant under the left rear flank of 2×10^6 human renal A498 cells (Figures 1 and 2), human renal ACHN cells (Figures 3 and 4), or human renal G402 cells (Figures 5 and 6). 3 to 6 weeks were allowed for the tumors to become established, as indicated. The size criteria for acceptance into the study was 0.05 to 0.50 cubic centimeters. The mice were given total weekly doses of PEG2-IFN α 2a or unmodified IFN α 2a of 30, 60, 120 or 300 μ g. In the case of PEG2-IFN α 2a the mice were treated one time per week (Monday) with 30, 60, 120 or 300 μ g of PEG2-IFN α 2a per treatment. In the case of unmodified IFN α 2a the mice were treated three times per week (Monday, Wednesday, Friday) with 10, 20, 40 or 100 μ g of IFN α 2a per treatment. The duration of treatment was 4 to 5 weeks depending on tumor aggressiveness. Tumor volumes were measured every Monday prior to treatments.

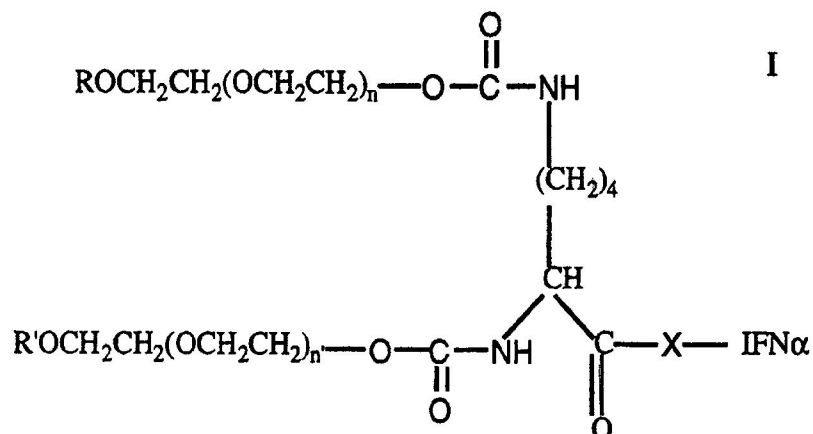
Results: PEG2-IFN α 2a showed a marked reduction in A498 tumor size as compared to unmodified IFN α 2a for all weekly dosage levels tested, at 7 days, 14 days, 21 days and 28 days after the beginning of treatment (Figures 1 and 2). Treatment continued for four weeks. Seven days after treatment was discontinued three mice in each group were sacrificed. In the three mice treated with PEG2-IFN α 2a no residual tumor was observed. In mice treated with unmodified IFN α 2a the A498 tumor weight was 1.28 grams, 0.62 grams, and 1.60 grams respectively in each of three mice. The A498 tumor weight was 2.32 grams, 2.37 grams, and 1.94 grams in each of three control mice. At 80 days after the end of the four week treatment period the existence of tumors was determined by palpation in seven mice. All seven mice were free of tumor tissue by palpation.

PEG2-IFN α 2a showed a significant reduction in ACHN tumor size as compared to unmodified IFN α 2a for weekly dosage levels of 60, 120, and 300 μ g, at 14 days, 21 days, 28 days and 35 days (Figures 3 and 4).

PEG2-IFN α 2a showed a significant reduction in G402 tumor size as compared to unmodified IFN α 2a for weekly dosage levels of 60 and 120 μ g, at 14 days, 21 days, 28 days and 35 days (Figures 5 and 6).

Claims

1. A physiologically active PEG-IFN α conjugate having the formula



wherein R and R' are independently lower alkyl; X is NH or O; n and n' are integers having a sum of from 600 to 1500; and the average molecular weight of the polyethylene glycol units in said conjugate is from about 26,000 daltons to about 66,000 daltons.

2. A conjugate of claim 1 wherein the molecular weight of the polyethylene glycol units is from about 35,000 to about 45,000 daltons.
3. A conjugate of claim 2 wherein the molecular weight of the polyethylene glycol units is about 40,000 daltons.
4. A conjugate of claim 1 wherein R and R' are methyl.
5. A conjugate of claim 1 wherein X is NH.
6. A conjugate of claim 1 wherein the IFN α is IFN α 2a.
7. A conjugate of claim 1 wherein the average sum of n and n' is 850 to 1000.
8. A conjugate of claim 1 wherein R and R' are methyl; X is NH; IFN α is IFN α 2a; and one or both of n and n' is 420.
9. A conjugate of claim 1 wherein R and R' are methyl; X is NH; IFN α is IFN α 2a; and one or both of n and n' is 520.
10. A conjugate of claim 1 which has greater antiproliferative activity than IFN α and less antiviral activity than IFN α .
11. A method for producing a PEG-IFN α conjugate having an increased antiproliferative activity and decreased antiviral activity as compared to IFN α , which method consists of covalently linking a reagent of Formula II to IFN α to produce said PEG-IFN α conjugate.
12. Pharmaceutical compositions comprising a PEG-IFN α conjugate as claimed in any one of claims 1-10 and a therapeutically inert carrier.
13. Pharmaceutical compositions for the treatment or prophylaxis of immunomodulatory disorders such as neoplastic diseases or infectious diseases comprising a PEG-IFN α conjugate as claimed in any one of claims 1-10 and a therapeutically inert carrier.
14. The use of a PEG-IFN α conjugate according to any one of claims 1-10 for the manufacture of medicaments for use in the treatment or prophylaxis of illnesses.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US98/07634 (22) International Filing Date: 28 April 1998 (28.04.98) (30) Priority Data: 08/839,101 29 April 1997 (29.04.97) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors: GLUE, Paul; 13 Allens Corner Road, Flemington, NJ 08822 (US). CUTLER, David, L.; 4 Windsor Way, Morristown, NJ 07960 (US). AFFRIME, Melton, B.; 2 Horseshoe Drive, Flemington, NJ 08822 (US). (74) Agents: McLAUGHLIN, Jaye, P. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: POLYETHYLENE GLYCOL-INTERFERON ALPHA CONJUGATES FOR THERAPY OF INFECTION (57) Abstract A method comprising administering a PEG ₁₂₀₀₀ -IFN alpha conjugate to an individual afflicted with a viral infection susceptible of treatment with interferon alpha, preferably chronic hepatitis C, is disclosed.		

as Intron® A available from Schering Corporation, Kenilworth, N.J., interferon alfa-2a such as Roferon® A available from Hoffmann-La Roche, Nutley, N.J.

U.S. Patent Nos. 4,695,623 and 4,897,471 disclose human leukocyte interferon polypeptides, referred to as consensus interferon, which have amino
5 acid sequences which include common or predominant amino acids found in each position among naturally-occurring interferon alpha subtype polypeptides.

Conditions that can be treated in accordance with the present invention are generally those that are susceptible to treatment with interferon alpha. For example, susceptible conditions include conditions which would
10 respond positively or favorably as these terms are known in the medical arts to interferon alpha-based therapy. For purposes of the invention, conditions that can be treated with interferon alpha therapy include those conditions in which treatment with an interferon alpha shows some efficacy, but which may not be treatable with interferon alpha because the negative side effects outweigh the
15 benefits of the treatment. For example, side effects accompanying alpha therapy have virtually ruled out treatment of Epstein Barr virus using interferon alpha. Practice of the invention results in substantially reduced or eliminated side effects as compared to conventional interferon alpha treatment.

Exemplary conditions which can be treated with interferon include
20 but are not limited to cell proliferation disorders, in particular cancer (e.g., hairy cell leukemia, Kaposi's sarcoma, chronic myelogenous leukemia, multiple myeloma, basal cell carcinoma and malignant melanoma, ovarian cancer, cutaneous T cell lymphoma), and viral infections. Without limitation, treatment with interferon may be used to treat conditions which would benefit from
25 inhibiting the replication of interferon-sensitive viruses. Viral infections which may be treated in accordance with the invention include hepatitis A, hepatitis B, hepatitis C, other non-A/non-B hepatitis, herpes virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex, human herpes virus type 6 (HHV-6), papilloma, poxvirus, picornavirus, adenovirus, rhinovirus, human T lymphotropic

CLAIMS

1. A method of treating a viral infection susceptible to treatment with interferon alpha comprising administering an amount of PEG₁₂₀₀₀-IFN alpha to a mammal in need of such treatment, which amount is effective to treat said viral infection while reducing or eliminating adverse side effects normally associated with administration of interferon alpha.

2. A method of treating hepatitis C viral infections in mammals which comprises administering an amount of PEG₁₂₀₀₀-interferon alpha to mammals in need of such treating while substantially reducing or eliminating adverse side effects normally associated with administering interferon alpha.

3. The method of claim 2, wherein the PEG₁₂₀₀₀-IFN alpha is PEG₁₂₀₀₀-IFN alpha-2b.

4. The method of claim 2, wherein the PEG₁₂₀₀₀-IFN alpha is PEG₁₂₀₀₀-IFN alpha-2a.

5. The method of claim 2, wherein the amount of PEG₁₂₀₀₀-IFN alpha administered is at least about 0.25 µg/kg/week.

6. The method of claim 2, wherein the amount of PEG₁₂₀₀₀-IFN alpha administered is about 0.25 µg/kg to about 1.5 µg/kg/week.

7. A method of treating hepatitis C viral infections in mammals which comprises administering at least about 0.25 µg/kg of PEG₁₂₀₀₀-interferon alpha-2b to a mammal in need of such treating.

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8. The method of claim 7, wherein at least about 0.25 $\mu\text{g/kg}$ of PEG₁₂₀₀₀-interferon alpha-2b is administered per week.

5 9. The method of claim 7, wherein about 1.5 $\mu\text{g/kg}$ of PEG₁₂₀₀₀-interferon alpha-2b is administered per week.

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(21) International Application Number: PCT/US94/13207 (22) International Filing Date: 10 November 1994 (10.11.94) (30) Priority Data: 08/150,643 10 November 1993 (10.11.93) US (71) Applicant: ENZON, INC. [US/US]; 40 Kingsbridge Road, Piscataway, NJ 08854 (US). (72) Inventors: GILBERT, Carl, W.; 26 Hampton Court, Basking Ridge, NJ 07920 (US). CHO, Myung-Ok; 166A Cedar Lane, Highland Park, NJ 08901 (US). (74) Agents: MERCANTI, Michael, M. et al.; Steinberg, Raskin & Davidson, 1140 Avenue of the Americas, New York, NY 10036 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i>
(54) Title: IMPROVED INTERFERON POLYMER CONJUGATES (57) Abstract A process is disclosed for preparing long-acting alpha interferon-containing compositions. Alpha interferon is contacted with a relatively small molar excess of a substantially non-antigenic polymer in the presence of a surfactant to preserve bioactivity. Isolation of the desired conjugate species having optimal activity is also disclosed.		

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conjugates are useful for, among other things, treating interferon-susceptible conditions or conditions which would respond positively or favorably as these terms are known in the medical arts to interferon-based therapy. Thus, without limitation, the interferon conjugates can be used to treat conditions which would benefit from the inhibiting replication of interferon-sensitive viruses. In addition, the conjugates can be used to modify various immune responses including inhibition of antibody response to antigenic challenge, inhibition of hypersensitivity reactions, regulation of NK cell activity enhancement of cytotoxic T cell activity, modulate prostaglandin production and enhance phagocytosis by macrophages.

Additional conditions in which the IFN-polymer conjugates can be used include hairy cell leukemia, venereal or genital warts (condylomata acuminata), AIDS-Related Kaposi's sarcoma, hepatitis and hepatitis-like viral conditions including hepatitis-B and chronic hepatitis non-A, non-B/C.

The amount of the α -IFN polymer conjugate administered to treat the conditions described above is based on the IFN activity of the polymeric conjugate. It is an amount that is sufficient to significantly affect a positive clinical response. The maximal dose for mammals including humans is the highest dose that does not cause clinically-important side effects. For purposes of the present invention, such clinically important side effects are those which would require cessation of therapy due to severe flu-like symptoms, central nervous system depression, severe gastrointestinal disorders, alopecia, severe pruritus or rash. Substantial white and/or red blood cell and/or liver enzyme abnormalities or anemia-like conditions are also dose limiting.

Naturally, the dosages of the various α IFN compositions will vary somewhat depending upon the α IFN

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moiety and polymer selected. In general, however, the conjugate is administered in amounts ranging from about 100,000 to about several million IU/m² per day, based on the mammal's condition. The range set forth above is illustrative and those skilled in the art will determine the optimal dosing of the conjugate selected based on clinical experience and the treatment indication.

The α IFN-polymer conjugates of the present invention can be included in one or more suitable pharmaceutical compositions for administration to mammals. The pharmaceutical compositions may be in the form of a solution, suspension, tablet, capsule or the like, prepared according to methods well known in the art. It is also contemplated that administration of such compositions will be chiefly by the parenteral route although oral or inhalation routes may also be used depending upon the needs of the artisan.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention.

EXAMPLE 1

Preparation of α IFN-PEG₅₀₀₀ in presence of SDS (0.1%)

In this example, recombinant α IFN-2b, (α IFN), a product of the Schering Corporation, Kenilworth, New Jersey was conjugated with activated polyethylene glycol-N-succinimide carbonate (SC-PEG) as described in U.S. patent No. 5,122,614. The polymer had a molecular weight of about 5000.

36 mg of the α IFN was dialyzed into 0.1 molar sodium phosphate pH 7.5 using a Centricon-10 (a product of the Amicon Corporation of Beverly, Mass.). The final

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concentration of r α IFN was about 3 mg/ml. 0.1 ml of 10% SDS was added to the r α IFN and was allowed to incubate at room temperature for 10 minutes. Thereafter, 42 mg of SC-PEG₅₀₀₀ was added to the protein-SDS solution and stirred at room temperature for two hours and then quenched with glycine. Next, the reaction mixture was dialyzed into 10 mM sodium phosphate pH 8 to fractionate the PEGylated IFN using a Centricon-30.

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EXAMPLE 2

Preparation of r α IFN-PEG₁₂₀₀₀ in presence of SDS (0.1%)

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In this Example, the steps of Example 1 were repeated except that the polyethylene glycol had a molecular weight of about 12000. Reaction steps were exactly the same to provide the PEG₁₂₀₀₀ conjugate.

EXAMPLE 3

Fractionation of 2PEG₅₀₀₀r α IFN

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In this Example the conjugates prepared in accordance with Example 1 were fractionated to obtain the desired 2-PEG₅₀₀₀ fraction. The PEG- α IFN in sodium phosphate buffer was loaded onto a QHD anion exchange column. The 2-PEG fraction was eluted with a gradient from 0 to 400 mM sodium chloride in 10 mM phosphate pH 8. The 2-PEG fraction was verified with using size exclusion chromatography and SDS-Page.

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EXAMPLE 4

Fractionation of 2PEG₁₂₀₀₀r α IFN

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The polymer conjugates of Example 2 were fractionated in the manner described in Example 3 and verified in the same manner.

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EXAMPLES 5-8

In these examples, additional preparations of PEG₁₂₀₀₀- α IFN were prepared as described previously except that no surfactant was used. The samples were tested for retained activity and PEG number. The results are provided below in the table.

Table 1

PREPARATION	ACTIVITY (CPE) % OF CONTROL	PEG #
Example 6	26	1.2
Example 7	26	1.3
Example 8	24	1.0

EXAMPLE 9

Comparative Data

In this example, the product of Example 3, (SDS-2-PEG₅₀₀₀- α IFN), 2-PEG₅₀₀₀- α IFN made in the absence of a surfactant and unconjugated α IFN were tested. Activity was determined using a CPE assay with EMC virus challenging A549 human lung carcinoma cells. Circulating life was determined using an average value obtained from the blood of 3 rats in a group receiving 1 million units, with time points taken over 7 days.

Table 2

	ACTIVITY (%)	VIRAL PROTECTION ASSAY IC ₅₀ (pg/ml)	CIRCULATING HALF LIFE α PHASE (HRS.)
A. IFN-SDS 2-PEG ₅₀₀₀	69	2.2	5.8
B. IFN-PEG ₅₀₀₀	30	4.0	6.8
C. IFN	100	1.5	0.17

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This data clearly shows the advantages of the inventive process. Retained activity is over twice as great as that obtained using standard techniques.

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EXAMPLE 10

In this example, various pharmacokinetic data was generated using the various 2PEG- α IFN conjugates shown below prepared according to the methods described above. These samples were compared to unmodified IFN according to the protocol set out in Table 3. Sample B was prepared with SDS.

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Table 3
Retained Activity

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SAMPLE	PEG MOLECULAR WEIGHT	CPE ACTIVITY (% CONTROL)
A	5,000	35
B	5,000	69
C	12,000	26
D	12,000	26

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For example:

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Table 4
Pharmacokinetic Protocol

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ANIMALS: Sprague Dawley (3 rates/time point)

DOSE: 10×10^6 UN IFN/rat

ROUTE: Subcutaneous (S.C.)

DRUG: 2-PEG-IFN α 's 5,000 and 12,000 mol. wt. PEG

TIME POINTS: 0 min., 5 min., 15 min., 30 min., 1 hr., 2 hr., 4 hr., 8 hr., 24 hr., 48 hr., 5 days, and 7 days following drug administration.

ASSAY: CPE Assay using serum samples in an EMC virus and A549 human lung carcinoma.

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89**WHAT IS CLAIMED IS:**

1. A process for preparing a long-acting alpha-interferon-containing composition, comprising contacting an alpha interferon with a substantially non-antigenic polymer in the presence of a surfactant under conditions sufficient to effect conjugation of said alpha interferon and said polymer.

2. The process of claim 1, wherein said polymer is present in a molar excess with respect to said alpha interferon.

3. The process of claim 2, wherein said polymer molar excess is from about 1 to about 8-fold.

4. The process of claim 3, wherein said polymer molar excess is from about 1.5 to about 7-fold.

5. The process of claim 4, wherein said polymer molar excess is from about 1.75 to about 5-fold.

6. The process of claim 1, wherein said polymer comprises a polyalkylene oxide.

7. The process of claim 6, wherein said polyalkylene oxide comprises an alkyl terminal.

8. The process of claim 6, wherein polyalkylene oxide is polyethylene glycol.

9. The process of claim 7, wherein said alkyl-terminated polyalkylene oxide is a monomethyl-terminated polyethylene glycol, (mPEG).

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10. The process of claim 1, wherein said substantially non-antigenic polymer has a molecular weight of from about 200 to about 35,000.

11. The process of claim 10, wherein said substantially non-antigenic polymer has a molecular weight of from about 1,000 to about 15,000.

12. The process of claim 11, wherein said substantially non-antigenic polymer has a molecular weight of from about 2,000 to about 12,500.

13. The process of claim 1, wherein said polymer is selected from the group consisting of dextran, polyvinyl pyrrolidones, polyacryl amides, polyvinyl alcohols and carbohydrate-based polymers.

14. The process of claim 1, wherein said surfactant is ionic.

15. The process of claim 14, wherein said surfactant comprises sodium dodecyl sulfate (SDS).

16. The process of claim 14, wherein said ionic surfactant is selected from the group consisting of lithium dodecyl sulfate, quaternary ammonium compounds, taurocholic acid, caprylic acid, decane sulfonic acid and mixtures thereof.

17. The process of claim 1, wherein said surfactant is selected from the group consisting of polyoxyethylene sorbitans, polyoxyethylene ethers and mixtures thereof.

18. The process of claim 14, wherein said surfactant is present in an amount from about 0.01-0.5%.

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19. The process of claim 18, wherein said surfactant is present in an amount of from about 0.05 to about 0.5%.

20. The process of claim 19, wherein said surfactant is present in an amount of from about 0.075 to about 0.25%.

21. The process of claim 1, further comprising isolating the polymer conjugated-alpha interferon species containing from about one to about four polymeric strands.

22. The process of claim 21, further comprising separating the polymer conjugated-alpha interferon species containing from about one to about three polymeric strands.

23. The process of claim 22, further comprising separating the polymer conjugated-alpha interferon species containing about two polymeric strands.

24. The process of claim 9, wherein said mPEG is activated with succinimidyl carbonate.

25. The process of claim 9, wherein said mPEG is activated with succinimidyl succinate.

26. The process of claim 9, wherein said mPEG is activated with a hydrazine moiety.

27. The process of claim 1, wherein said alpha interferon is isolated from a mammalian source.

28. The process of claim 27, wherein said mammalian alpha interferon is human alpha interferon.

29. The process of claim 27, wherein said mammalian alpha interferon is ruminant alpha interferon.

30. The process of claim 29, wherein said ruminant alpha interferon is bovine alpha interferon.

31. The process of claim 27, wherein said mammalian alpha interferon is porcine alpha interferon.

32. A product prepared according to the process of claim 1.

33. A product prepared according to the process of claim 21.

34. A method of treating an interferon-susceptible condition in mammals, comprising administering an effective amount of a composition prepared according to the process of claim 1.

35. A method of treating an interferon-susceptible condition in mammals, comprising administering an effective amount of a composition prepared according to the process of claim 21.

36. An alpha-interferon-conjugate, comprising an alpha-interferon having attached thereto an amount of a substantially non-antigenic polymer so that said conjugate has a $T_{\max}$ and an AUC which are substantially greater than unmodified alpha-interferon measured under the same conditions.

37. The conjugate of claim 36, wherein said conjugate has a $T_{\max}$ at least about 4 times greater than unmodified alpha-interferon measured under the same conditions.

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38. The conjugate of claim 37, wherein said conjugate has a $T_{\max}$ at least about 8 times greater than unmodified alpha-interferon measured under the same conditions.

39. The conjugate of claim 36, wherein said conjugate has an AUC at least about 2 times that of unmodified alpha-interferon measured under the same conditions.

40. The conjugate of claim 39, wherein said conjugate has an AUC at least about 10 times that of unmodified alpha-interferon measured under the same conditions.

41. The conjugate of claim 36, wherein said substantially non-antigenic polymer is polyethylene glycol.

42. The conjugate of claim 41, wherein said polyethylene glycol has a molecular weight of about 12,000.

43. An alpha-interferon-conjugate, comprising an alpha-interferon having attached thereto a polyalkylene oxide derivative, said conjugate having at least about 10% of the activity of unmodified alpha-interferon measured under the same conditions, a $T_{\max}$ of at least about 2 hours alpha phase when said conjugate is administered subcutaneously in a mammal.

44. An alpha-interferon-conjugate, comprising an alpha-interferon having attached thereto a polyalkylene oxide derivative, said conjugate having at least about 10% of the activity of unmodified alpha-interferon measured under the same conditions, and a $T_{1/2}$ of about 5 hours alpha phase when said conjugate is administered subcutaneously in a mammal.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

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Bogotá, D.C., Abril 20 de 2005

Doctor

ALVARO CORREA ORDÓÑEZ

ASUNTO	Radicación No.	00 024 855
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	15724
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 41 a 56 y el capítulo reivindicatorio de los folios 57 a 59 de la solicitud en estudio.

2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 a 20 se refieren a un método para tratar un paciente que consiste en administrar una dosis de interferón alfa modificado con PEG y opcionalmente citarabina.

El problema planteado en esta solicitud es la necesidad de proporcionar un método para tratar pacientes que sufren leucemia mielocítica crónica (CML).

Para resolver este problema técnico la solicitud en estudio proporciona un método que consiste en administrar una dosis de interferón alfa modificado con PEG y opcionalmente citarabina.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 38/21.

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 09 288 369 de abril 8 de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Excepciones a la Patentabilidad

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El artículo 20 de la Decisión 486 establece: *"No serán patentables: d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Las reivindicaciones 1 a 20 se refieren a un método para tratar un paciente que consiste en administrar una dosis de interferón alfa modificado con PEG y opcionalmente citarabina.

Se observa que el método que consiste en administrar una dosis de interferón alfa modificado con PEG y opcionalmente citarabina de las reivindicaciones 1 a 20, no es patentable de acuerdo con la norma citada, que especifica que *los métodos terapéuticos para el tratamiento humano o animal* no son patentables.

En conclusión, el método que consiste en administrar una dosis de interferón alfa modificado con PEG y opcionalmente citarabina, de las reivindicaciones 1 a 20, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

4. Conclusión

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha 05 MAYO 2005

CONCEPTO TÉCNICO No. 593	EXAMINADOR TÉCNICO Código 202007
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