(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 386 106 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **02.03.94** (51) Int. Cl.5: **A61K 37/66**, A61K 47/00

(21) Application number: **88910211.7**

(22) Date of filing: **01.11.88**

(86) International application number:
PCT/US88/03883

(87) International publication number:
WO 89/04177 (18.05.89 89/11)

(54) GAMMA INTERFERON FORMULATION.

(30) Priority: **03.11.87 US 116434**

(43) Date of publication of application:
12.09.90 Bulletin 90/37

(45) Publication of the grant of the patent:
02.03.94 Bulletin 94/09

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP-A- 008 079
EP-A- 0 258 683

Patent Abstr. of Japan, vol. 9, no. 28 (C-264)(1751), 06.02.85

Patent Abstr. of Japan, vol. 11, no. 139 (C-420)(2586), 07.05.87

(73) Proprietor: **GENENTECH, INC.**
460 Point San Bruno Boulevard
South San Francisco California 94080(US)

(72) Inventor: **HWANG-FELGNER, Jiin-Yu**
Vical/10955
John J. Hopkins, No. 2
San Diego, CA 92121(US)
Inventor: **JONES, Richard, E.**
870 Los Robles Avenue
Palo Alto, CA 94306(US)
Inventor: **MAHER, James, F.**
2503 E. Albany g
Broken Arrow, OK 74014(US)

(74) Representative: **Armitage, Ian Michael et al**
MEWBURN ELLIS
2 Cursitor Street
London EC4A 1BQ (GB)

EP 0 386 106 B1

Description

Field of the Invention

This invention relates to a stable biologically active gamma-interferon liquid formulation.

Background of the Invention

Immune or gamma-interferon was originally classified on a physical basis as Type II Interferon due to its lability to acid treatment and/or heating to 56°C. This operational classification distinguished it from virus-induced or Type I Interferons (alpha and beta) which, in general, are not acid or heat labile. As a result of the widespread availability of specific antisera against each of the major interferon classes (alpha, beta, and gamma), classification and distinction of each type is now usually made by serological or immunological methods. Despite this, gamma-interferon preparations are still identified as such by their rapid inactivation upon acid treatment. See, The Interferon System, 2nd edition, W.E. Stewart II, Springer-Verlag, New York, 1981.

Gamma-interferon has been employed in clinical studies for many years. The methods currently available for preparing gamma-interferon dosage forms comprises lyophilizing the gamma-interferon in combination with other ingredients for reconstitution with an appropriate diluent at the time of use. Because gamma-interferon is known to be acid labile, it has traditionally been handled at neutral or slightly alkaline pH. See, for example, U.S. Patent No. 4,499,014 which discloses reactivation of a lyophilized acidic gamma-interferon solution to a pH of 6 to 9. U.K. Patent Application GB 2119313A discloses lyophilized formulations of gamma-interferon reconstituted at pH 7.5. Neutral or slightly alkaline solutions of higher concentrations of gamma-interferon are unusable as injectable formulations because of the immediate formation of a visible precipitate. Such precipitates may cause thrombosis on administration or decrease potency. European Patent Application Publication No. 0196203 discloses reconstitution of lyophilized gamma-interferon to a pH of 4 to 6.0. Japanese Kokai 61-277633 discloses an interferon composition including a surfactant, but does not suggest the avoidance of lyophilization. EP-A-80879 discloses lyophilized interferon formulations.

An object of the present invention is to provide a biologically active, stable liquid formulation of gamma-interferon for use in injectable applications. Another object of this invention is to provide a formulation which does not require prior lyophilization of a gamma-interferon composition. It is another object of this invention to prevent dimer and oligomer formation consequent to lyophilization of gamma-interferon. Yet another object of this invention is to provide a liquid formulation containing biologically active gamma-interferon having improved stability. Still another object of this invention is to provide a liquid formulation permitting storage for a long period of time in a liquid state facilitating storage and shipping prior to administration. Still another object of this invention is to reduce aggregation of gamma-interferon, particularly that associated with heating. Another object of this invention is to provide a liquid formulation resistant to fluctuations in temperature. Yet another object of this invention is the elimination from the preparation of a bulking or stabilizing agent such as human serum albumin (HSA). Still another object of this invention is to reduce potential contamination by other proteins and other blood contaminants which may be associated with human serum albumin. Yet another object of this invention is to provide a liquid formulation which is easily made and administered having eliminated lyophilization and reconstitution steps. Yet another object of this invention is to provide a pharmaceutical composition containing non-lyophilized gamma interferon that can be produced less expensively.

Summary of the Invention

The objects of this invention are accomplished by a liquid pharmaceutical composition comprising an effective amount of biologically active non-lyophilized gamma-interferon. The liquid pharmaceutical composition may additionally include a buffer capable of maintaining the pH of the liquid formulation within the range of 4.0 to 6.0, a stabilizing agent and a nonionic detergent. In a preferred embodiment of the liquid formulation of this invention the pH will be in the range of 4.5 to 5.5, preferably at pH 5.0. The gamma-interferon of this invention is not lyophilized but, rather, once prepared from sources using methods known to the ordinarily skilled artisan is included directly in the formulation of this invention. The stabilizing agent of this invention is typically a polyhydric sugar alcohol. It was not appreciated until this invention that a liquid formulation of gamma-interferon could be made which retains biological activity, has a long shelf-life and can be administered therapeutically without lyophilization and reconstitution. In addition, it was not appreciated until this invention that a liquid formulation of gamma-interferon at pH of from 4 to 6 would

decrease aggregation, reduce thermal unfolding of the protein and maintain biological activity. It was also not appreciated until this invention that a non-lyophilized liquid formulation at pH 5.0 could have an extended shelf life. Accordingly, the invention is directed to a liquid pharmaceutical composition comprising an effective amount of non-lyophilized gamma interferon for therapeutic administration. In a preferred embodiment of the invention, the liquid pharmaceutical composition is sterile. The liquid pharmaceutical composition according to the invention is preferably suitable for storage for more than two weeks.

Detailed Description

Gamma interferon and its methods of preparation, including synthesis in recombinant cell culture, are well known (EP 77, 670A and 146, 354A). Included within the scope of gamma-interferon are gamma interferon from recombinant or native sources as well as gamma-interferon variants, such as amino acid sequence variants, e.g., Cys-Tyr-Cys or desCys-Tyr-Cys amino terminal species. Also included are other insertions, substitutions or deletions of one or more amino acid residues, glycosylation variants, un-glycosylated gamma-interferons, organic and inorganic salts and covalently modified derivatives of gamma-interferon. The effective amount of gamma-interferon to be formulated in the liquid composition is selected based on several variables, including the disease to be treated and therapeutic regimen. Generally the gamma-interferon has an activity in a standard bioassay in the range of $1x10^6$ to $2x10^7$ U/mg protein or more.

Examples of the polyhydric sugar alcohols to be used as the stabilizer in the present invention to insure isotonicity of the composition are those of trihydric or higher, such as glycerin, erythritol, arabitol, xylitol, sorbitol and mannitol. These polyhydric sugar alcohols can be used alone or in a combination thereof. In view of stabilization of interferon, the sugar alcohol is formulated in an amount of 1% to 25% by weight and preferably, 2% to 5% by weight taking into account the amounts of the other ingredients.

The organic acid buffers to be used in the present invention to maintain the pH in the range of about 4.0 to 6.0 and preferably from 4.5 to 5.5 can be conventional buffers of organic acids and salts thereof such as citrate buffers (e.g., monosodium citrate-disodium citrate mixture, citric acid-trisodium citrate mixture, citric acid-monosodium citrate mixture, etc.), succinate buffers (e.g., succinic acid-monosodium succinate mixture, succinic acid-sodium hydroxide mixture, succinic acid-disodium succinate mixture, etc.), tartrate buffers (e.g., tartaric acid-sodium tartrate mixture, tartaric acid-potassium tartrate mixture, tartaric acid-sodium hydroxide mixture, etc.), fumarate buffers (e.g., fumaric acid-monosodium fumarate mixture, fumaric acid-disodium fumarate mixture, monosodium fumarate-disodium fumarate mixture, etc.), gluconate buffers (e.g., gluconic acid-sodium gluconate mixture, gluconic acid-sodium hydroxide mixture, gluconic acid-potassium gluconate mixture, etc.), oxalate buffers (e.g., oxalic acid-sodium oxalate mixture, oxalic acid-sodium hydroxide mixture, oxalic acid-potassium oxalate mixture, etc.), lactate buffers (e.g., lactic acid-sodium lactate mixture, lactic acid-sodium hydroxide mixture, lactic acid-potassium lactate mixture, etc.) and acetate buffers (e.g., acetic acid-sodium acetate mixture, acetic acid-sodium hydroxide mixture, etc.). It is noteworthy that inorganic acid buffers such as phosphate buffers which have been used traditionally do not maintain the pH of the liquid formulation at the desired pH.

Examples of the non-ionic detergents include such surfactants as pluronics, for example, polysorbate 80 and polysorbate 20. The non-ionic detergent is present in a range of .05 mg/mL with a preferred range of about .07 to .2 mg/mL and a most preferred amount of about 0.1 mg/mL.

The liquid formulation of this invention at a pH of 4 to 6, preferably 4.5 to 5.5 and most preferably at pH 5, demonstrates limited aggregation upon warming. Rather than being labile the liquid formulation of this invention is stable for prolonged periods. The formulation of this invention may be stored in a liquid state at various temperatures. A preferred storage temperature is in the range of -20°C to 30°C with a most preferred temperature storage range of about between 2° and 8°C. All of the components are important for maintenance of biological activity and physical stability. Furthermore, the liquid formulation of this invention will retain biological activity and physical stability without freezing. This avoids potential aggregation upon thawing.

The following examples illustrate the present invention,

Example 1

Liquid Formulation

Human recombinant gamma-interferon (20 x 10^6 U/mg) was formulated by adding either 1.0 or 0.2 mg/mL to: succinic acid (0.27 mg/mL); disodium succinate (0.73 mg/ml); mannitol (40 mg/mL); polysorbate

20 (0.1 mg/mL); and a sufficient quantity of Water For Injection (USP). This liquid formulation was found to exhibit a long shelf life when maintained at a storage temperature of about between 2° and 8°C in a liquid state. The succinate buffer maintained the liquid formulation at pH 5.0. The non-ionic detergent prevented aggregation during shipping and handling. The sugar rendered the formulation isotonic without the need for the addition of salts, which have been shown to cause aggregation of gamma-interferon. And further, the sugar appears to stabilize the pharmaceutical composition of this invention (compare the succinate/mannitol lyophilized formulation to the HSA/phosphate lyophilized formulation).

The liquid formulation of this invention using 0.2 mg/mL of non-lyophilized gamma-interferon was compared to two other lyophilized formulations of gamma-interferon. As seen in Table I below, the loss of bioactivity reflected in the rate constants was ten-fold greater for the succinate/mannitol lyophilized formulation. and five-fold greater for HSA/phosphate lyophilized formulation than the liquid formulation of this invention. These changes in the bioactivity are reflected in the rate constant which is the slope of the line resulting from a plot of the natural logarithm of the loss of bioactivity of the gamma-interferon formulation versus time. Bioactivity was measured using a viral protection assay known to the ordinarily skilled artisan. The lyophilized compositions were stored in lyophilized form and were reconstituted at various times to determine the bioactivity remaining in the lyophilized preparation. The shelf life of the liquid formulation of this invention was considerably greater than that of the lyophilized formulations. The greater shelf life of the liquid formulation relative to the lyophilized formulation listed in Table 1 shows that the liquid formulation of this invention retains biological activity ten times longer than the lyophilized compositions.

Table 1

Comparative Stability of Gamma-Interferon Formulated at 0.2 mg/mL[1]			
Formulation	Study (months)	Rate Constant X 10^{-3}	Relative Shelf Life (days)[2]
Succinate/Mannitol Lyophilized	6	2.854	1
Succinate/Mannitol Liquid	4	0.205	10
HSA/Phosphate Lyophilized[3]	3	1.038	5

[1] Based on real time 5°C data.

[2] A comparison of the relative stability based on the bioactivity of the three formulations with the succinate/mannitol lyophilized composition being arbitrarily set at 1.

[3] This formulation was prepared by mixing 0.20 mg lyophilized gamma-interferon, 10 mg HSA, 5 mM sodium phosphate pH 7.0 and reconstituted with 0.9% saline.

A similar comparative study was carried out for the liquid formulation of this invention using 1.0 mg/mL of non-lyophilized human recombinant gamma-interferon. Once again, as shown in Table 2, the loss of bioactivity was greater for the lyophilized formulation than for the liquid formulation of this invention. Table 2 also shows that the shelf life of the liquid formulation of this invention was three times greater than that of the lyophilized formulation.

Table 2

Comparative Stability of Gamma-Interferon Formulated at 1.0 mg/mL[1]			
Formulation	Study Time (months)	Rate Constant X 10^{-3}	Relative Shelf Life (days)[2]
Succinate/Mannitol Lyophilized	14	0.485	1
Succinate/Mannitol Liquid	14	0.179	3

[1] Based on real time 5°C data.

[2] A comparison of the relative stability based on the bioactivity of the two formulations with the succinate/mannitol lyophilized composition being arbitrarily set at 1.

Claims

1. A liquid pharmaceutical composition suitable for extended storage in a liquid state, comprising an effective amount of non-lyophilized gamma-interferon and excluding human serum albumin, which composition has not been frozen or lyophilized.

2. A liquid pharmaceutical of claim 1 which additionally includes a buffer capable of maintaining the pH of the liquid composition within the range of 4.0 to 6.0, a stabilizing agent and a non-ionic detergent.

3. A liquid pharmaceutical composition of claim 2 wherein the buffer is an organic acid buffer.

4. A liquid pharmaceutical composition of claim 3 wherein the organic acid buffer is selected from the group consisting of citrate, succinate, tartrate, fumarate, gluconate, oxalate, lactate and acetate.

5. A liquid pharmaceutical composition of claim 2 wherein the stabilizing agent is a polyhydric sugar alcohol.

6. A liquid pharmaceutical composition of claim 5 wherein the polyhydric sugar alcohol is selected from the group consisting of glycerin, erythritol, arabitol, xylitol, sorbitol and mannitol.

7. A liquid pharmaceutical composition of claim 6 wherein the sugar alcohol is added in an amount of about 1% to 25% by weight based on the composition.

8. A liquid pharmaceutical composition of claim 6 wherein the sugar alcohol is added in an amount of about 2% to 5% by weight based on the composition.

9. A liquid pharmaceutical composition of claim 2 wherein the non-ionic detergent is selected from the group consisting of polysorbate 20 and polysorbate 80.

10. A liquid pharmaceutical composition of claim 2 wherein the pH of the liquid composition is in the range of 4.5 to 5.5.

11. A liquid pharmaceutical composition of claim 2 wherein the pH of the liquid composition is at a pH of 5.0.

12. A liquid pharmaceutical composition of claim 2 which is sterile.

13. A liquid pharmaceutical composition of claim 2 which is isotonic to blood.

14. A liquid pharmaceutical composition of claim 1 suitable for storage for more than two weeks.

15. A method of making and storing a liquid pharmaceutical composition comprising preparing an effective amount of non-lyophilized gamma interferon, and storing such composition in the absence of human serum albumin in an aqueous state without freezing or lyophilizing for a period in excess of about four months.

16. A liquid pharmaceutical composition suitable for extended storage in a aqueous state, consisting essentially of an effective amount of non-lyophilized gamma interferon, a buffer capable of maintaining the pH of the liquid composition within the range of 4.0 to 6.0, a stabilizing agent and a non-ionic detergent.

Patentansprüche

1. Flüssige pharmazeutische Zusammensetzung, die zur langfristigen Lagerung in flüssigem Zustand geeignet ist und eine wirksame Menge an nicht-lyophilisiertem gamma-Interferon umfaßt und menschliches Serumalbumin ausschließt, welche Zusammensetzung nicht eingefroren oder lyophilisiert worden ist.

2. Flüssige pharmazeutische Zusammensetzung nach Anspruch 1, die zusätzlich einen Puffer, der fähig ist, den pH-Wert der flüssigen Zusammensetzung innerhalb des Bereichs von 4,0 bis 6,0 zu halten, einen Stabilisator und einen nicht-ionischen oberflächenaktiven Stoff enthält.

3. Flüssige pharmazeutische Zusammensetzung nach Anspruch 2, worin der Puffer ein organischer Säurepuffer ist.

4. Flüssige pharmazeutische Zusammensetzung nach Anspruch 3, worin der organische Säurepuffer aus der Gruppe ausgewählt ist, die aus Zitrat, Succinat, Tartrat, Fumarat, Glukonat, Oxalat, Laktat und Acetat besteht.

5. Flüssige pharmazeutische Zusammensetzung nach Anspruch 2, worin der Stabilisator ein mehrwertiger Zuckeralkohol ist.

6. Flüssige pharmazeutische Zusammensetzung nach Anspruch 5, worin der mehrwertige Zuckeralkohol aus der Gruppe ausgewählt ist, die aus Glycerin, Erythrit, Arabit, Xylit, Sorbit und Mannit besteht.

7. Flüssige pharmazeutische Zusammensetzung nach Anspruch 6, worin der Zuckeralkohol in einer Menge von etwa 1 bis 25 Gew.-%, bezogen auf die Zusammensetzung, hinzugefügt ist.

8. Flüssige pharmazeutische Zusammensetzung nach Anspruch 6, worin der Zuckeralkohol in einer Menge von etwa 2 bis 5 Gew.-%, bezogen auf die Zusammensetzung, hinzugefügt ist.

9. Flüssige pharmazeutische Zusammensetzung nach Anspruch 2, worin der nichtionische oberflächenaktive Stoff aus der Gruppe ausgewählt ist, die aus Polysorbat 20 und Polysorbat 80 besteht.

10. Flüssige pharmazeutische Zusammensetzung nach Anspruch 2, worin der pH-Wert der flüssigen Zusammensetzung im Bereich von 4,5 bis 5,5 liegt.

11. Flüssige pharmazeutische Zusammensetzung nach Anspruch 2, worin der pH-Wert der flüssigen Zusammensetzung ein pH-Wert von 5,0 ist.

12. Flüssige pharmazeutische Zusammensetzung nach Anspruch 2, die steril ist.

13. Flüssige pharmazeutische Zusammensetzung nach Anspruch 2, die zu Blut isotonisch ist.

14. Flüssige pharmazeutische Zusammensetzung nach Anspruch 1, die zur Lagerung für mehr als zwei Wochen geeignet ist.

15. Verfahren zur Herstellung und Lagerung einer flüssigen pharmazeutischen Zusammensetzung, umfassend das Herstellen einer wirksamen Menge an nichtlyophilisiertem Gammainterferon und das Lagern einer solchen Zusammensetzung in Abwesenheit von menschlichem Serumalbumin in wässerigem Zustand ohne Frieren oder Lyophilisieren für einen Zeitraum über etwa vier Monaten.

16. Flüssige pharmazeutische Zusammensetzung, die zur langfristigen Lagerung in wässerigem Zustand geeignet ist und im wesentlichen aus einer wirksamen Menge an nichtlyophilisiertem Gammainterferon, einem Puffer, der fähig ist, den pH-Wert der flüssigen Zusammensetzung im Bereich von 4,0 bis 6,0 zu halten, einem Stabilisator und einem nichtionischen Detergens besteht.

Revendications

1. Composition pharmaceutique liquide apte à un stockage prolongé à l'état liquide, comprenant une quantité efficace de gamma-interféron non lyophilisé et dépourvue de sérum-albumine humaine, composition qui n'a pas été congelée ou lyophilisée.

2. Composition pharmaceutique liquide suivant la revendication 1, qui comprend en outre un tampon capable de maintenir le pH de la composition liquide dans l'intervalle de 4,0 à 6,0, un stabilisant et un détergent non ionique.

3. Composition pharmaceutique liquide suivant la revendication 2, dans laquelle le tampon est un tampon à base d'un acide organique.

4. Composition pharmaceutique liquide suivant la revendication 3, dans laquelle le tampon à base d'acide organique est choisi dans le groupe consistant en un citrate, un succinate, un tartrate, un fumarate, un gluconate, un oxalate, un lactate et un acétate.

5. Composition pharmaceutique liquide suivant la revendication 2, dans laquelle le stabilisant est un sucre-alcool polyhydroxylique.

6. Composition pharmaceutique liquide suivant la revendication 5, dans laquelle le sucre-alcool polyhydroxylique est choisi dans le groupe consistant en le glycérol, l'érythritol, l'arabitol, le xylitol, le sorbitol et le mannitol.

7. Composition pharmaceutique liquide suivant la revendication 6, dans laquelle le sucre-alcool est ajouté en une quantité d'environ 1 % à 25 % en poids, sur la base de la composition.

8. Composition pharmaceutique liquide suivant la revendication 6, dans laquelle le sucre-alcool est ajouté en une quantité d'environ 2 % à 5 % en poids, sur la base de la composition.

9. Composition pharmaceutique liquide suivant la revendication 2, dans laquelle le détergent non ionique est choisi dans le groupe consistant en le polysorbate 20 et le polysorbate 80.

10. Composition pharmaceutique liquide suivant la revendication 2, dont le pH est compris dans la plage de 4,5 à 5,5.

11. Composition pharmaceutique liquide suivant la revendication 2, dont le pH est égal à 5,0.

12. Composition pharmaceutique liquide suivant la revendication 2, qui est stérile.

13. Composition pharmaceutique liquide suivant la revendication 2, qui est isotonique vis-à-vis du sang.

14. Composition pharmaceutique liquide suivant la revendication 1, apte à un stockage pendant plus de deux semaines.

15. Procédé de préparation et de stockage d'une composition pharmaceutique liquide, comprenant la préparation d'une quantité efficace de gamma-interféron non lyophilisé, et le stockage de cette composition en l'absence de sérum-albumine humaine, à l'état aqueux, sans congélation ou lyophilisation, pendant un temps supérieur à environ quatre mois.

16. Composition pharmaceutique liquide apte à un stockage prolongé à l'état aqueux, consistant essentiellement en une quantité efficace de gamma-interféron non lyophilisé, un tampon capable de maintenir le pH de la composition liquide dans la plage de 4,0 à 6,0, un stabilisant et un détergent non ionique.

REGISTER ENTRY FOR EP0386106

European Application No EP88910211.7 filing date 01.11.1988

Priority claimed:
03.11.1987 in United States of America - doc: 116434

PCT EUROPEAN PHASE
PCT Application PCT/US88/03883 Publication No WO89/04177 on 18.05.1989

Designated States BE CH DE FR GB IT LI LU NL SE AT

Title GAMMA INTERFERON FORMULATION.

Applicant/Proprietor
GENENTECH, INC., 460 Point San Bruno Boulevard, South San Francisco California 94080, United States of America [ADP No. 50241215001]

Inventors
JIIN-YU HWANG-FELGNER, Vical/10955 John J. Hopkins, No. 2, San Diego, CA 92121, United States of America [ADP No. 57775793001]

E. RICHARD JONES, 870 Los Robles Avenue, Palo Alto, CA 94306, United States of America [ADP No. 57775801001]

F. JAMES MAHER, 2503 E. Albany g, Broken Arrow, OK 74014, United States of America [ADP No. 57775819001]

Classified to
A61K

Address for Service
MEWBURN ELLIS, 2 Cursitor Street, LONDON, EC4A 1BQ, United Kingdom [ADP No. 00000109001]

EPO Representative
IAN MICHAEL ARMITAGE, MEWBURN ELLIS & CO. 2/3 Cursitor Street, London EC4A 1BQ, United Kingdom [ADP No. 50329846001]

Publication No EP0386106 dated 12.09.1990
Publication in English

Examination requested 26.03.1990

Patent Granted with effect from 02.03.1994 (Section 25(1)) with title GAMMA INTERFERON FORMULATION.

27.01.1994 MEWBURN ELLIS, 2 Cursitor Street, LONDON, EC4A 1BQ, United Kingdom [ADP No. 00000109001]

registered as address for service
Entry Type 8.11 Staff ID. ER1 Auth ID. AA

28.01.1994 Notification from EPO of change of EPO Representative details from
IAN MICHAEL ARMITAGE, MEWBURN ELLIS & CO. 2/3 Cursitor Street,
London EC4A 1BQ, United Kingdom [ADP No. 50329846001]
to
IAN MICHAEL ARMITAGE, MEWBURN ELLIS 2 Cursitor Street, London EC4A
1BQ, United Kingdom [ADP No. 50329846001]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

09.04.1994 Notification of change of Address For Service address of
MEWBURN ELLIS, 2 Cursitor Street, LONDON, EC4A 1BQ, United Kingdom
[ADP No. 00000109001]
to
MEWBURN ELLIS, York House, 23 Kingsway, LONDON, WC2B 6HP, United
Kingdom [ADP No. 00000109001]
dated 14.03.1994. Written notification filed on GB2270363
Entry Type 7.3 Staff ID. BH Auth ID. HEO

**** END OF REGISTER ENTRY ****

RENEWAL DETAILS

PUBLICATION NUMBER EP0386106

PROPRIETOR(S)

GENENTECH, INC., 460 Point San Bruno Boulevard, South San Francisco California 94080, United States of America

DATE FILED 01.11.1988

DATE GRANTED 02.03.1994

DATE NEXT RENEWAL DUE 01.11.1995

DATE NOT IN FORCE

DATE OF LAST RENEWAL 24.10.1994

YEAR OF LAST RENEWAL 07

STATUS PATENT IN FORCE

**** END OF REPORT ****