

COPY

ARNOLD & PORTER LLP

Rachel L. Adams, Ph.D.
Rachel_Adams@aporter.com
202.942.5512
202.942.5999 Fax
555 Twelfth Street, NW
Washington, DC 20004-1206

February 9, 2005

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent No. 5,677,278
Issued: October 14, 1997
Title: **Truncated Keratinocyte Growth Factor (KGF) Having
Increased Biological Activity**
Applicants: Denis J. GOSPODAROWICZ *et al.*
Atty. Docket No.: 14483.005

Sir:

The following documents are forwarded herewith for appropriate action by the U.S. Patent and Trademark Office (USPTO):

1. Request for Extension of Patent Term Under 35 U.S.C. §156 (in duplicate);
2. Request for Extension of the Term of United States Patent No. 5,677,278 Under 35 U.S.C. §156 for Kepivance™ (Palifermin), including Authorization to Rely Upon Marketing Activities in Request for Extension of Patent Term Under 35 U.S.C. §156; Exhibit A: copy of U.S. Patent No. 5,677,278; Exhibit B: copy of Maintenance Fee Statement; and Exhibit C: copy of Request for Certificate of Correction (together with two duplicate copies as required under 37 C.F.R. § 1.740(b) and two additional duplicate copies pursuant to MPEP § 2753); and
3. Return postcard.

Please stamp the postcard with the filing date of these documents and return it to our courier.

Authorization to charge the \$1,120.00 fee for the filing of this application is given in the accompanying documents.

Respectfully submitted,



David R. Marsh (Reg. No. 41,408)
Rachel L. Adams (Reg. No. 54,660)

Attachments

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE : U.S. Patent No. 5,677,278
ISSUED: October 14, 1997
TO: GOSPODAROWICZ, *et al.*
FOR: TRUNCATED KERATINOCYTE
GROWTH FACTOR (KGF) HAVING
INCREASED BIOLOGICAL
ACTIVITY
FROM: SERIAL NO. 08/410,941
FILED: March 27, 1995

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

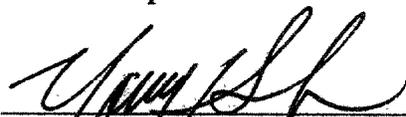
Dear Sirs,

Transmitted herewith are the application papers of Chiron Corporation dated February 8, 2005, for extension of U.S. Patent No. 5,677,278 under 35 U.S.C. §156, based on the regulatory review period for Kepivance™ (palifermin), together with two duplicate copies as required under 37 C.F.R. § 1.740 (b) and two additional duplicate copies of the application pursuant to M.P.E.P. §2753, for a total of four copies and one original.

As set forth under 37 C.F.R. §1.20(j), please charge the sum of \$1,120.00 to Deposit Account No. 03-1664 for the filing of this application for extension of patent term. Also, please charge any underpayment, or any additional fee that may be required, or credit any overpayment, to Deposit Account No. 03-1664. Two copies of this paper are enclosed.

Respectfully submitted,
Chiron Corporation

Date: Feb. 8, 2005



Young J. Suh (Reg. No. 41,337)
Attorney for Applicant

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE : U.S. Patent No. 5,677,278
ISSUED: October 14, 1997
TO: GOSPODAROWICZ, *et al.*
FOR: TRUNCATED KERATINOCYTE
GROWTH FACTOR (KGF) HAVING
INCREASED BIOLOGICAL
ACTIVITY
FROM: SERIAL NO. 08/410,941
FILED: March 27, 1995

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**REQUEST FOR EXTENSION OF THE TERM OF
UNITED STATES PATENT NO. 5,677,278 UNDER 35 U.S.C. §156
FOR KEPIVANCE™ (PALIFERMIN)**

Dear Sirs,

Chiron Corporation, a corporation organized and existing under the laws of the State of Delaware, and having a place of business at 4560 Horton Street, Emeryville, California, 94662-8097, United States of America, represents that it is the assignee of Letters Patent of the United States No. 5,677,278 granted to Gospodarowicz, *et al.* on October 14, 1997, for Truncated Keratinocyte Growth Factor (KGF) Having Increased Biological Activity, by virtue of assignments, recorded in the United States Patent and Trademark Office (hereinafter referred to as "the Patent Office") on August 12, 1993, at Reel 6638, Frame 0596.

Pursuant to the provisions of 37 C.F.R. §1.730, applicant hereby applies for an extension of the term of Patent No. 5,677,278 under 35 U.S.C. §156 of 1417 days, based on the materials set forth herein and in the accompanying papers.

In the materials which follow herein, numbered paragraphs (1) through (15) correspond to paragraphs (1) through (15) of 37 C.F.R. §1.740(a).

(1) The approved product is Kepivance™ (palifermin). Kepivance™ is a human keratinocyte growth factor (KGF) produced by recombinant DNA technology in *Escherichia coli* (*E coli*). Kepivance™ is a water-soluble, 140 amino acid protein with a molecular weight of 16.3 kilodaltons. It differs from endogenous human KGF in that the first 23 N-terminal amino acids have been deleted to improve protein stability.

Molecular Weight:

The molecular weight is 16.3 kilodaltons.

Structural Formula:

The amino acid sequence is numbered in accordance with endogenous, full length human KGF. Amino acids 1-54 of endogenous, full length human KGF are absent in Kepivance™ (palifermin). That is, the first 23 amino acids of endogenous, mature human KGF (which are amino acid numbers 32-54 of the endogenous, full length human KGF) are absent in Kepivance™. The CAS registry number for palifermin is 162394-19-6.

	Ser	Tyr	Asp	Tyr	Met	Glu	Gly	Gly	Asp	Ile	
	55					60					
Arg	Val	Arg	Arg	Leu	Phe	Cys	Arg	Thr	Gln	Trp	Tyr
65				70					75		80
Lys	Arg	Gly	Lys	Val	Lys	Gly	Thr	Gln	Glu	Met	Lys
			85					90			95
Ile	Met	Glu	Ile	Arg	Thr	Val	Ala	Val	Gly	Ile	Val
	100					105				110	
Val	Glu	Ser	Glu	Phe	Tyr	Leu	Ala	Met	Asn	Lys	Glu
	115					120				125	
Ala	Lys	Lys	Glu	Cys	Asn	Glu	Asp	Cys	Asn	Phe	Lys
	130				135					140	
Glu	Asn	His	Tyr	Asn	Thr	Tyr	Ala	Ser	Ala	Lys	Trp
145				150					155		160
Gly	Glu	Met	Phe	Val	Ala	Leu	Asn	Gln	Lys	Gly	Ile
			165					170			175
Lys	Lys	Thr	Lys	Lys	Glu	Gln	Lys	Thr	Ala	His	Phe
	180						185				190
Ile	Thr										
194											

We note that the term "product," for purposes of patent term extension for a drug product, is defined as "the active ingredient of a new drug, antibiotic drug, or human biological product...including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." 35 U.S.C. § 156(f)(2). Nothing in this application should be construed as limiting the term product for purposes of the requested patent term extension to the specific form of human keratinocyte growth factor approved in Kepivance™.

(2) Kepivance™ (palifermin) was subject to regulatory review under Section 351 of the Public Health Service Act, 42 U.S.C. § 262.

(3) Kepivance™ (palifermin) received permission for commercial marketing or use under section Section 351 of the Public Health Service Act, 42 U.S.C. § 262, on December 15, 2004.

(4) The active ingredient in Kepivance™ (palifermin) is a human keratinocyte growth factor (KGF) produced by recombinant DNA technology in *Escherichia coli* (*E coli*). That active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. § 1.720(f). The last day on which this application could be submitted is February 11, 2005.

(6) The patent for which an extension is being sought is identified as follows:

Inventors: Dennis J. Gospodarowicz and Frank R. Masiarz
Patent No.: 5,677,278
For: TRUNCATED KERATINOCYTE GROWTH FACTOR (KGF)
HAVING INCREASED BIOLOGICAL ACTIVITY
Issued: October 14, 1997
Expires: October 14, 2014

(7) A copy of U.S. Patent No. 5,677,278, the patent for which an extension is being sought, is attached hereto as EXHIBIT A.

(8) One maintenance fee payment for U.S. Patent No. 5,677,278 was made to keep the patent in force beyond four years from its issue date (a copy of the receipt of such payment is included herewith as EXHIBIT B). On January 11, 2005, Applicants filed a Request for Certificate of Correction of Office Mistake for U.S. Patent No. 5,677,278 (a copy of the Request for Certificate of Correction is included herewith as EXHIBIT C). Pursuant to 37 C.F.R. § 1.740(a)(8), Applicants will submit as a supplement to this Request for Extension of Patent Term Under 35 U.S.C. § 156 a copy of any Certificate of Correction, if granted, for U.S. Patent No. 5,677,278.

(9) Patent No. 5,677,278 claims the approved product. Claims 1-6 and 10 claim the approved product.

Claim 1 of Patent No. 5,677,278 reads on Kepivance™ because:

Kepivance™ is a keratinocyte growth factor fragment that exhibits at least a 2-fold increase in mitogenic activity as compared to a mature, recombinant, full-length keratinocyte growth factor, wherein the fragment lacks the first 23 N-terminal amino acid residues of the mature, full-length keratinocyte growth factor but retains the remainder of the molecule.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

- An exemption under subsection (i) of section 505 of the Federal Food, Drug and Cosmetic Act became effective for Kepivance™ (palifermin) on December 2, 1995, following receipt by the Food and Drug Administration of an Investigational New Drug (“IND”) Application, identified by FDA as BB-IND 6370, on November 2, 1995.
- A Biologics License Application (“BLA”) under section 351 of the Public Health Service Act for Kepivance™ (palifermin) was completed as follows:
 - Reviewable Unit 1 of the BLA was submitted to FDA on May 14, 2004¹
 - Reviewable Unit 2 of the BLA was submitted on June 15, 2004.This BLA was assigned the number 125103/0
- BLA No. 125103/0 was approved on December 15, 2004.

¹ Because this application was reviewed by FDA as part of its “Fast Track” program, the BLA was submitted in two stages. We believe that the first submission date constitutes the date that this application “was initially submitted” for purposes of 35 U.S.C. § 156(g). Accordingly, we have calculated the proposed period of extension on that basis. However, if it is determined that the date of the second submission is the appropriate one to be used for this purpose, 16 days should be subtracted from the period of extension we have calculated.

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities follows:

The investigational new drug application (“IND”) for this drug was submitted on November 1, 1995. It was received by FDA on November 2 and became effective on December 2, 1995. Amgen conducted a series of clinical investigations of this drug. On December 31, 2003, FDA granted fast track designation to this product. The first reviewable unit of the biologic license application (“BLA”) for this product was submitted on May 14, 2004, with a subsequent submission of the second reviewable unit on June 17, 2004. The BLA was approved on December 15, 2004.

The following chart identifies significant events and communications of substance with the FDA concerning this product:

<u>Date</u>	<u>Regulatory Event</u>
Nov. 1, 1995	Submission of IND
Nov. 7, 1995	FDA letter acknowledging receipt of IND on Nov. 2, 1995 and assigning identifier BB-IND 6370 to IND
Dec. 2, 1995	Effective Date of IND
Dec. 13, 1995	Submission of study protocols 950224 & 950225
Jan. 31, 1996	Submission of study protocols 950275 & 950226
May 6, 1996	Submission of proposed revised clinical development plan
Jul. 17, 1997	Submission of study protocol 960136
Jul. 31, 1997	Submission of study protocol 970147
Sept. 19, 1997	Submission of study protocol 960189
Dec. 10, 1997	Submission of study protocol 970189
Mar. 19, 1998	Submission of study protocol 970149
Dec. 22, 1998	Submission of study protocol 980231
Sept. 30, 1999	Meeting with FDA to discuss clinical development of KGF
Dec. 17, 1999	Teleconference with FDA to discuss clinical development issues

Sept. 5, 2000	End of Phase 3 Meeting with FDA
Aug. 6, 2001	Type C Meeting with FDA
Sept. 7, 2001	Teleconference with FDA to discuss proposed quality of life trial
Nov. 16, 2001	FDA letter explaining clinical hold on proposed study
Dec. 26, 2001	Submission of response to clinical hold
Mar. 28, 2002	FDA letter explaining clinical hold on proposed study
Apr. 24, 2002	Submission of response to clinical hold
May 10, 2002	FDA letter lifting partial clinical hold
Aug. 23, 2002	Submission of study protocol 20010192
Oct. 30, 2002	Submission of study protocols 20010182 & 990123
Sept. 21, 2003	pre-BLA Meeting with FDA
Dec. 2, 2003	CMC Meeting with FDA
Dec. 5, 2003	Submission of request for fast track designation
Dec. 31, 2003	FDA letter granting fast track designation
May 14, 2004	Submission of initial components of BLA
Jun. 10, 2004	Meeting with FDA Review Division
Jun. 15, 2004	Submission of additional components of BLA
Jul. 9, 2004	Submission of immunogenicity data
Jul. 20, 2004	Submission of revised immunogenicity data
Aug. 13, 2004	FDA notification that the Kevivance BLA is accepted for filing
Aug. 27, 2004	FDA letter containing questions regarding immunogenicity data and inspectional readiness at the drug substance manufacturing facility
Oct. 15, 2004	Teleconference with FDA concerning review schedule

Nov. 15, 2004 FDA discipline review letter for module 4 the BLA received by Amgen

Dec. 15, 2004 Amgen receives FDA approval letter

(12) In the opinion of the Applicant, U.S. Patent No. 5,677,278 is eligible for an extension under 35 U.S.C. §156. The length of extension claimed is 1417 days.

The length of extension of term of Patent No. 5,677,278 of 1417 days claimed by applicant was determined according to the provisions of 37 C.F.R. §1.775 as follows:

- According to 37 C.F.R. §1.775(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of 37 C.F.R. §1.775.
- According to 37 C.F.R. §1.775(c), the regulatory review period is the sum of: (A) the number of days in the period beginning on the date the exemption under subsection 505 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the BLA was initially submitted under Section 351 of the Public Health Service Act; and (B) the number of days in the period beginning on the date the BLA was initially submitted under Section 351 of the Public Health Service Act and ending on the date the BLA was approved. The exemption under subsection 505(i) of the Federal Food, Drug and Cosmetic Act became effective on Dec. 2, 1995; and the BLA was approved on December 15, 2004. Hence the regulatory review period under 37 C.F.R. §1.775(c) is the sum of the period from December 2, 1995 to May 14, 2004 and from May 14, 2004 to December 15, 2004. This is the sum of 3301 days.
- According to 37 C.F.R. §1.775(d)(1)(i), the number of days in the regulatory review period which were on and before the date on which the patent issued must be subtracted. Patent No. 5,677,278 issued on October 14, 1997. Subtraction of the period on or before October 14, 1997 leaves a reduced regulatory review period from October 15, 1997 to May 14, 2004 and from May 14, 2004 to December 15, 2004. This is the sum of 2403 days and 215 days, which is 2618 days.
- 37 C.F.R. §1.775(d)(1)(ii) does not apply.
- According to 37 C.F.R. §1.775 (d)(1)(iii), the regulatory review period must then be reduced by one-half of the days remaining in the period defined in 37 C.F.R. §1.775(c)(1). This is one-half of 2403 days, which, disregarding half days, is 1201 days. After subtraction, this now leaves a reduced regulatory review period of 1202 days plus 215 days, which is 1417 days.
- According to 37 C.F.R. §1.775(d)(2), the reduced regulatory review period of 1417 days must be added to the expiration date of Patent No. 5,677,278, i.e., October 14, 2014. This gives a date of August 31, 2018.
- According to 37 C.F.R. §1.775(d)(3), 14 years must be added to the date of approval of the approved product. This gives a date of December 15, 2018.
- According to 37 C.F.R. §1.775(d)(4), the earlier of these dates must be selected. The earlier date of these dates is August 31, 2018.
- The provisions of 37 C.F.R. §1.775(d)(5) apply to this application because Patent No. 5,677,278 issued after September 24, 1984. Pursuant to 37 C.F.R. §1.775(d)(5)(i), five (5) years are added to the expiration date of Patent No. 5,677,278 (October 14, 2014) giving a date of October 14, 2019. According to 37 C.F.R. §1.775(d)(5)(ii), the dates obtained pursuant to 37 C.F.R.

§1.775(d)(5)(i) and 37 C.F.R. §1.775(d)(4) are compared and the earlier date is selected. The date calculated according to 37 C.F.R. §1.775(d)(4) above is August 31, 2018. Therefore, the earlier of these dates is August 31, 2018. Applicant is entitled to an extension of term of Patent No. 5,677,278 until August 31, 2018, i.e., an extension of 1417 days from original expiration date of October 14, 2014.

- The provisions of 37 C.F.R. §1.775(d)(6) do not apply because Patent No. 5,677,278 issued on October 14, 1997, after September 24, 1984.

(13) Applicant acknowledges a duty to disclose to the Director of United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought to the term of Patent No. 5,677,278.

(14) The prescribed fee under 37 C.F.R. §1.20(j) for receiving and acting on this application for patent term extension is to be charged to Deposit Account No. 03-1664.

(15) Please direct all inquiries and correspondence relating to this application for patent term extensions as follows:

David R. Marsh
Arnold & Porter LLP
555 Twelfth Street, N.W.
Washington, D.C. 20004-1206
(202) 942-5068 telephone
(202) 942-5999 facsimile

Pursuant to 37 C.F.R. §1.740(b), two duplicate copies of these application papers are enclosed herewith. Pursuant to M.P.E.P. §2753 an additional two copies of the application are also enclosed herewith. Accordingly, a total of one original application for patent term extension of Patent No. 5,677,278 and four copies of the application are submitted herewith.

Applicant respectfully requests prompt and favorable action on the merits of this application for extension of the term of Letters Patent No. 5,677,278 of 1417 days, based on the regulatory review period for Kepivance™ (palifermin).²

Respectfully submitted,
Chiron Corporation

Date: Feb. 8, 2005



Young J. Suh (Reg. No. 41,337)
Attorney for Applicant

² As noted in footnote 1, *supra*, this total would be reduced by 16 days, to 1401 days, if the PTO were to conclude that this application was not "initially submitted" for purposes of 35 U.S.C. § 156(g) until the second reviewable unit of that BLA was submitted on June 15, 2004.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE : U.S. Patent No. 5,677,278
ISSUED: October 14, 1997
TO: GOSPODAROWICZ, *et al.*
FOR: TRUNCATED KERATINOCYTE
GROWTH FACTOR (KGF) HAVING
INCREASED BIOLOGICAL
ACTIVITY
FROM: SERIAL NO. 08/410,941
FILED: March 27, 1995

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

AUTHORIZATION TO RELY UPON MARKETING ACTIVITIES
IN REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Dear Sirs,

Pursuant to M.P.E.P. § 2752, Amgen Inc., a corporation organized and existing under the laws of the State of Delaware, and having a place of business at One Amgen Center Drive, Thousand Oaks, California, 91320, United States of America, hereby authorizes Chiron Corporation to rely upon the activities of Amgen Inc. before the Food and Drug Administration during the regulatory review period for Kepivance™ (palifermin) in its request for extension of patent term under 35 U.S.C. § 156 of U.S. Patent No. 5,677,278, granted to Gospodarowicz, *et al.* on October 14, 1997, and assigned to Chiron Corporation by virtue of assignments recorded in the United States

Patent and Trademark Office on August 12, 1993, at Reel 6638, Frame 0596. Amgen Inc., effective December 23, 2002, is the licensee of Chiron Corporation with respect to U.S. Patent No. 5,677,278.

Respectfully submitted,
Amgen Inc.

Date: 2/7/05

A handwritten signature in black ink, consisting of stylized, overlapping letters that appear to be 'R', 'R', and 'R'.

Robert Ramos (Reg. No. 37,915)
Attorney for Marketing Applicant