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Attorneys for Plaintiffs
Immunex Corporation and
Amgen Manufacturing, Limited

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IMMUNEX CORPORATION; AMGEN MANUFACTURING, LIMITED; and HOFFMANN-LA ROCHE INC.;	)	Civil Action No. 16-1118 (CCC/MF)
Plaintiffs,	)	
v.	)	REDACTED VERSION
SANDOZ INC.; SANDOZ INTERNATIONAL GMBH; and SANDOZ GMBH;	)	
Defendants.	)	*Electronically Filed*

MEMORANDUM OF LAW IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Of Counsel:
Liza M. Walsh and David Pritikin

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Rules

Immunex Corporation and Amgen Manufacturing, Limited ("Immunex") respectfully submit this Memorandum of Law in support of Immunex's Motion for Summary Adjudication of Infringement Under 35 U.S.C. § 271(e)(2)(C).

I. INTRODUCTION

[redacted] Trial on infringement is not warranted, as the material facts are not disputed. Accordingly, Immunex seeks summary adjudication of a single issue: that Sandoz Inc. ("Sandoz") infringed claim 1 of US 8,722,631 ("the '631 Patent") when Sandoz submitted its biosimilar etanercept application to the FDA.

Section 271 of the patent statute identifies various types of acts constituting infringement. According to subsection (e)(2)(C), it is an act of infringement to submit an application to the FDA if the purpose of such submission is to obtain approval to engage in the commercial manufacture, use, or sale of a biosimilar biological product the use of which is claimed in a patent. In July of 2015, Sandoz did just that, and since February 26, 2016 the parties have been litigating this infringement.

In its biosimilar application, [redacted]

[redacted]. Sandoz's act of infringing claim 1 under § 271(e)(2)(C) is complete. Indeed, [redacted] Summary judgment is thus ripe.

Summary judgment is also appropriate. First, it streamlines issues for trial. Second, it determines the respective rights of the parties with respect to the '631 patent and with respect to the parties' [redacted] Stipulation, dkt. no. 96 (under seal). Entry of summary judgment on even a single claim of just one Immunex Patent will, under the plain terms of the parties' [redacted] Stipulation, [redacted] Thus, a ruling on this summary judgment motion provides certainty for the parties [redacted]

Immunex thus respectfully asks that the Court grant this motion.

II. LEGAL STANDARDS

When a movant shows that the material facts on an issue are undisputed, summary judgment is appropriate. FED. R. CIV. P. 56(a); *Celotex Corp. v. Catrett*, 477 U.S. 317, 322-23 (1986). To oppose a well-taken motion, the opponent must establish that there are material facts that a trial must resolve. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.,* 475 U.S. 574, 587 (1986). Metaphysical doubt, *id.* at 586, speculation, and conclusory allegations are not enough, *Ridgewood Bd. of Educ. v. N.E. ex rel. M.E.*, 172 F.3d 238, 252 (3d Cir. 1999).

Title 35 U.S.C. § 271 sets forth the acts that constitute patent infringement. Section 271(e)(2)(C), which was added by the BPCIA,[1] specifies that the filing of a biosimilar application is an act of infringement:

> (2) It shall be an act of infringement to submit—
>
> > (C) (i) with respect to a patent that is identified in the list of patents described in section 351(*l*)(3) of the Public Health Service Act (including as provided under section 351(*l*)(7) of such Act), an application seeking approval of a biological product,
>
> if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

[1] The Biologics Price Competition and Innovation Act of 2009 ("BPCIA") allowed for the filing of biosimilar applications by amending, *inter alia*, section 351 of the Public Health Service Act ("PHS Act"), codified at 42 U.S.C. § 262.

III. BACKGROUND

Sandoz submitted an application seeking approval of its etanercept under the PHS Act

On July 30, 2015, Sandoz submitted a Biologics License Application ("BLA 761042") seeking FDA approval for its proposed biosimilar of Immunex's Enbrel® (etanercept) biological product.[2] This included a letter stating:

[redacted][3]

Sandoz's BLA submission included a [redacted].[4]

[2] Statement of Undisputed Material Facts ("Undisputed Facts") ¶¶ 1-10, submitted herewith.

[3] Undisputed Facts ¶ 2. Sandoz [redacted]

[4] Sandoz's FDA submissions included [redacted]

Sandoz's BLA sought [redacted]

Sandoz's submitted BLA 761042 for the purpose of [redacted]

Sandoz [redacted] in its BLA Form FDA 356h: [redacted]

Sandoz listed and described these sought-after uses in its BLA label submission: [redacted]

[redacted] Undisputed Facts ¶¶ 9-13.

[5] In general medical parlance, [redacted] "psoriatic arthritis" is commonly abbreviated as "PsA" and "plaque psoriasis" is commonly abbreviated as "PsO."

[6] Undisputed Facts ¶ 5 (all highlighting added unless stated otherwise).

[7] Undisputed Facts ¶ 9.

[8] *Id.*

[9] *Id.*

Sandoz's BLA sought [redacted]

Sandoz's BLA label submission specified [redacted]

[redacted]

Immunex included the '631 patent in its PHS Section 351(l)(3) list of patents

On December 18, 2015, not later than sixty days after receiving Sandoz's purported disclosure pursuant to section 351(*l*)(2)(A) of the PHS Act, Immunex provided its list of patents under section 351(*l*)(3) of the PHS Act ("351(*l*)(3) list")

[10] Undisputed Facts ¶ 10.
[11] *Id.*

naming the '631 patent as one of the unexpired U.S. patents for which it believed infringement could reasonably be asserted against Sandoz.[12]

[redacted]

At no time in this litigation have any of the Defendants alleged that [redacted] as directed [redacted]. They have neither disputed that [redacted] nor asserted that any claim construction issue [redacted]

In their Invalidity and Non-Infringement Contentions, Defendants did not offer any dispute that [redacted]

[12] Undisputed Facts ¶ 14. The '631 patent will expire on August 13, 2019—20 years after the date the earliest nonprovisional application to which the '631 patent claims priority was filed. The FDA approved BLA 761042 on August 30, 2016. Undisputed Facts ¶ 11.
[13] Undisputed Facts ¶ 16.
[14] Undisputed Facts ¶ 17.

In claim construction, Defendants did not introduce any claim term disputes that they alleged would somehow change [redacted].

Prior to *Markman* briefing, the parties notified the Court of their agreement concerning the meaning of certain phrases in the Immunex Patents. There, Sandoz agreed that "TNFR:Fc" as used in the claims of those patents means "etanercept."[15]

IV. ARGUMENT

A. Sandoz Has Infringed '631 Patent Claim 1 as a Matter of law

1. Sandoz's submission sought approval under the PHS Act

One prerequisite to establishing Sandoz's infringement under § 271(e)(2)(C) is its submission of "an application seeking approval of a biological product" under the PHS Act. There is no dispute that Sandoz did this through its BLA 761042.[16]

2. Immunex identified the '631 patent in its PHS 351(*l*)(3) list

Another prerequisite to establishing infringement under § 271(e)(2)(C) is that the patent at issue must have been identified in the list of patents described in

[15] Undisputed Facts ¶ 23. [redacted]
Undisputed Facts ¶ 15.

[16] Undisputed Facts ¶¶ 1-2, 7.

§ 351(*l*)(3) of the PHS Act.[17] There is no dispute that Immunex identified the '631 patent to Sandoz in its 351(*l*)(3) list on December 18, 2015.[18]

3. Sandoz's submission sought approval for a claimed use

The prerequisites met, Sandoz infringed the patent under § 271(e)(2)(C) if its BLA was submitted for "the purpose of … obtain[ing] approval … to engage in the commercial manufacture, use, or sale of a … biological product … the use of which is claimed in a patent before the expiration of such patent." 35 U.S.C. § 271(e)(2)(C). Sandoz's communications to Immunex and its internal planning documents show [redacted][19]

Sandoz has indisputably infringed.

[17] § 351(*l*)(3) list is described in 42 U.S.C. § 262(*l*)(3)(A).
[18] Undisputed Facts ¶ 14.
[19] Undisputed Facts ¶ 19 (Sandoz June 14, 2013 letter stated "Sandoz Inc., has developed an etanercept product, biosimilar to Enbrel®, which they intend to market in the United States following necessary regulatory approvals."), ¶ 20 (Sandoz [redacted] ¶ 21 (Sandoz July 10, 2016 letter stated "Sandoz . . . expects . . . to receive FDA approval to market its product on August 30, 2016. Absent some agreement between the parties, Sandoz intends to begin commercial marketing of its product immediately thereafter.").

Claim 1 of the '631 Patent [redacted]

> 1. A method of treatment comprising administering a dose of TNFR:Fc to a patient having psoriatic arthritis and/or plaque psoriasis,
> wherein the dose is administered one time or two times per week, and
> wherein the dose administered is 25-50 mg or 50-100 mg, and
> wherein the dose is administered by subcutaneous injection.[20]

The BLA label Sandoz originally submitted [redacted] Thus, '631 patent claim 1 is not a claim that might be incidentally infringed [redacted]

[20] Undisputed Facts ¶ 22.

a. Sandoz's BLA submission directs [redacted]

Sandoz's proposed label submitted as part of its BLA for Defendants' etanercept directs [redacted].[21]

b. Sandoz's BLA submission directs [redacted]

Sandoz's proposed label submitted as part of its BLA for Defendants' etanercept directs that, [redacted].[22] The label [redacted]

Thus, [redacted] satisfies each and every limitation of claim 1 of the '631 patent.[23]

[21] Undisputed Facts ¶ 9; *see* pages 3-5, *supra*.
[22] Undisputed Facts ¶ 10; *see* pages 4-6, *supra*.
[23] Undisputed Facts ¶¶ 9-10; *see* pages 3-7, *supra*.

4. Claim construction is not necessary for this determination

Defendants' infringement contentions neither allege non-infringement of claim 1 of the '631 patent under 271(e)(2)(C) nor identify any issue related to claim construction that bears on such infringement.[24] Thus, no claim construction dispute need be addressed by this Court before rendering summary judgment of infringement because "it is not necessary for the Court to conduct a claim construction proceeding prior to deciding [the patentee]'s motion for partial summary judgment of literal infringement as [the defendant] has failed to identify terms that it believes need to be construed for purpose of literal infringement." *PacTool Int'l Ltd. v. Kett Tool Co*., 2010 WL 5174762, *2 (W.D. Wash. Dec. 15, 2010); *see also H2Ocean, Inc. v. Schmitt*, 2007 WL 2376233, *3 & n.3 (N.D. Fla. Aug. 15, 2007) (conclusion "that the plaintiff has established infringement as a matter of law" could "be reached without the court first holding a *Markman* hearing").

Because the claim construction issues briefed to the Court for the Immunex Patents implicate [redacted] not only is claim construction of the Immunex Patents

[24] Undisputed Facts ¶¶ 16-17; [redacted] *Id.* ¶ 18.

unnecessary for the present motion, it would be an impermissible advisory opinion. *Vivid Techs. v. Am. Sci. & Eng'g*, 200 F.3d 795, 803 (Fed. Cir. 1999) (courts should construe claims "only to the extent necessary to resolve the controversy" between parties); *Jang v. Boston Scientific Corp.*, 532 F.3d 1330, 1336 (Fed. Cir. 2008) ("Article III does not permit the courts to resolve issues when it is not clear that the resolution of the question will resolve a concrete controversy between interested parties.").

V. CONCLUSION

There is no genuine dispute as to any material fact that Sandoz's submission of BLA 761042 constitutes infringement of claim 1 of Immunex's '631 Patent. Defendants have never offered any evidence to the contrary, or indeed ever even alleged otherwise. Immunex is entitled to judgment as a matter of law that Sandoz has infringed claim 1 of the '631 Patent under § 271(e)(2)(C) and respectfully requests such relief from the Court.

_____

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September 12, 2017

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IN THE UNITED STATES DISTRICT COURT
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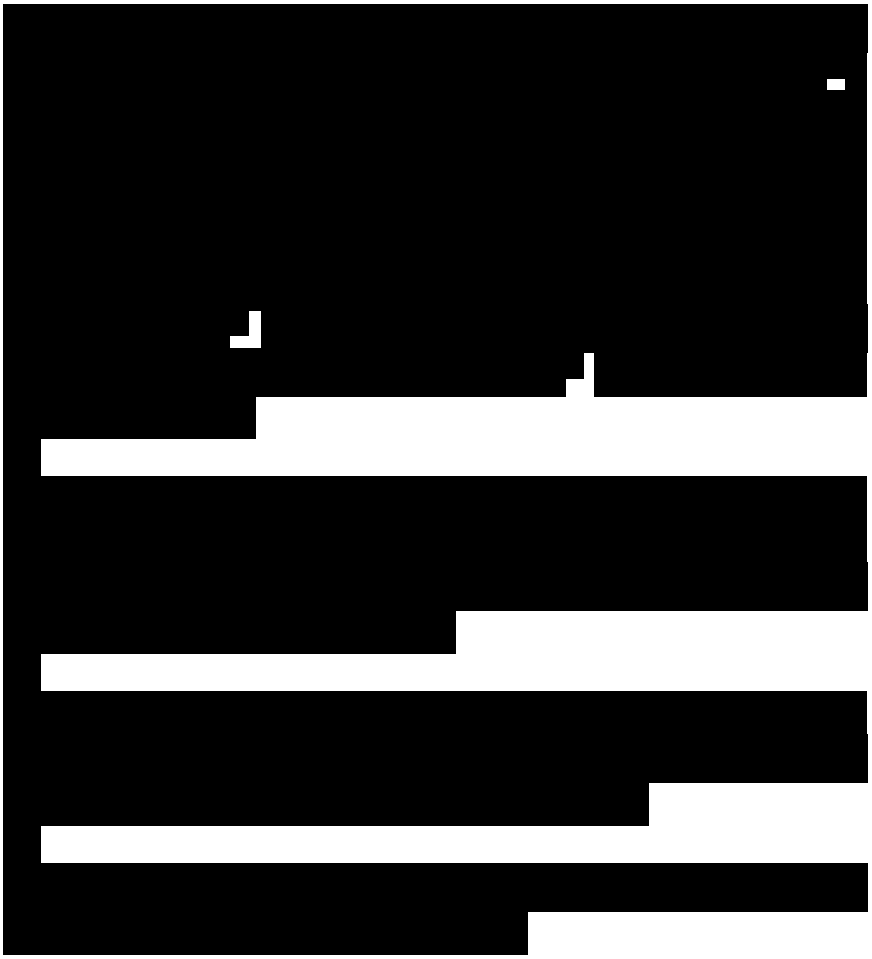
IMMUNEX CORPORATION; AMGEN MANUFACTURING, LIMITED; and HOFFMANN-LA ROCHE INC.;	)	Civil Action No. 16-1118 (CCC/MF)
Plaintiffs,	)	
v.	)	REDACTED VERSION
SANDOZ INC.; SANDOZ INTERNATIONAL GMBH; and SANDOZ GMBH;	)	
Defendants.	)	*Electronically Filed*

PLAINTIFFS' STATEMENT OF UNDISPUTED MATERIAL FACTS IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Pursuant to Local Civil Rule 56.1 the Plaintiffs set out the following undisputed material facts that support their Motion for Summary Judgment:

1. [redacted]

2. [redacted]



High Decl. ¶ 4, Ex. A at 1-3.

3. Sandoz submitted BLA 761042 for the purpose of obtaining approval for [redacted]

[redacted]

High Decl. ¶¶ 4, 8; Ex. A at 2; Ex. B at 1.

4. Immunex Corporation holds the BLA for Enbrel® and is the "reference product sponsor" for Enbrel® within the meaning of 42 U.S.C. § 262(*l*). High Decl. ¶ 28, Ex. J at 1.

5. [redacted]

High Decl. ¶ 8, Ex. B at 1.

6. Sandoz's BLA 761042, Form FDA 356h identified "Enbrel® (etanercept)" as [redacted] High Decl. ¶ 9, Ex. B at 1.

7. Sandoz's BLA 761042 stated [redacted]

[redacted] High Decl. ¶¶ 4, 9-10; Ex. A at 1-2; Ex. B at 1-2.

8. Sandoz is a "subsection (k) applicant" within the meaning of 42 U.S.C. § 262(*l*). High Decl. ¶¶ 4, 9-10; Ex. A at 1-2; Ex. B at 1-2.

9 [redacted]

High Decl. ¶ 14, Ex C at SAN-ETAN_0000624.

[redacted]

High Decl. ¶ 14, Ex C at SAN-ETAN_0000626.

[redacted]

High Decl. ¶ 14, Ex C at SAN-ETAN_0000626.

10. [redacted]

[redacted]

High Decl. ¶ 15, Ex. C at SAN-ETAN_0000626.

[redacted]

High Decl. ¶ 15, Ex. C at SAN-ETAN_0000624.

11. On August 30, 2016, FDA approved BLA 761042, including with the indications, usage, dosage and administration [redacted] High Decl. ¶ 30, Ex. L at SAN-ETAN_0187999, -171.

12. The approved label for Sandoz's product approved under BLA 761042 is publicly available. High Decl. ¶ 17, Ex. D.

13. With respect to Sandoz's etanercept's composition, properties, and requested indications and dosing regimens, the approved label is [redacted]

[redacted]. High Decl. ¶¶ 12-17; Ex. C at SAN-ETAN_0000624, SAN-ETAN_0000626; Ex. D at AMG-ENBNJ-00353756, AMG-ENBNJ-00353759.

14. On December 18, 2015, Immunex provided Sandoz, the biosimilar applicant of BLA 761042, with its list of patents under section 351(*l*)(3) of the PHS Act ("351(*l*)(3) list") naming the '631 patent as one of the unexpired U.S. patents for which it believed infringement could reasonably be asserted against Sandoz. High Decl. ¶ 19, Ex. F at 1.

15. According to Sandoz, etanercept is [redacted] High Decl. ¶ 25; Ex. C at SAN-ETAN_0000634; Ex. I at 2.

16. In their Invalidity and Non-infringement Contentions, Defendants did not dispute that [redacted] High Decl. ¶ 21, Ex. G at 283-84.

17. [redacted]

High Decl. ¶ 22, Ex. H at 1.

18. On July 27, 2017, [redacted]. High Decl. ¶ 18, Ex. E at 1.

19. In a letter from Sandoz to Amgen Inc. and Hoffman-La Roche, Inc. dated June 14, 2013, Sandoz stated "Sandoz Inc., has developed an etanercept product, biosimilar to Enbrel®, which they intend to market in the United States following necessary regulatory approvals." High Decl. ¶ 32, Ex. M at A1556.

20. A document produced by Sandoz in this action dated "[redacted] in reference to Sandoz's product submitted for approval in BLA 761042. High Decl. ¶¶ 33, 35, Ex. N at SAN-ETAN_0346012, SAN-ETAN_0346043.

21. In a letter from Sandoz Immunex Corp. dated July 10, 2016, Sandoz stated "Sandoz has filed an application for FDA approval of a Sandoz biosimilar

etanercept product, for which Immunex's ENBREL® is the reference product. Sandoz . . . expects . . . to receive FDA approval to market its product on August 30, 2016. Absent some agreement between the parties, Sandoz intends to begin commercial marketing of its product immediately thereafter." High Decl. ¶ 28, Ex. J at 1.

22. Claim 1 of U.S. Patent No. 8,722,631 recites "A method of treatment comprising administering a dose of TNFR:Fc to a patient having psoriatic arthritis and/or plaque psoriasis, wherein the dose is administered one time or two times per week, and wherein the dose administered is 25-50 mg or 50-100 mg, and wherein the dose is administered by subcutaneous injection." High Decl. ¶ 30, Ex. K.

23. In the context of the claims of the Immunex Patents, Sandoz agreed that "TNFR:Fc" means "etanercept." High Decl. ¶ 24, Ex. I at 2.

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IMMUNEX CORPORATION; AMGEN MANUFACTURING, LIMITED; and HOFFMANN-LA ROCHE INC.; Plaintiffs, v. SANDOZ INC.; SANDOZ INTERNATIONAL GMBH; and SANDOZ GMBH; Defendants.	**REDACTED VERSION** Civil Action No.: 2:16-cv-01118-CCC-MF **DECLARATION OF JAMES A. HIGH JR. SUPPORTING IMMUNEX'S MOTION FOR SUMMARY ADJUDICATION OF INFRINGEMENT UNDER 35 U.S.C. § 271(e)(2)(C)**

I, James A. High Jr., of full age, declare:

1. I am an attorney with the law firm Sidley Austin LLP, counsel of record for Immunex Corporation and Amgen Manufacturing, Limited (collectively, "Immunex") in this matter, and am a member in good standing of the State Bar of California and the District of Columbia Bar. I am admitted *pro hac vice* before this Court. The facts stated herein are true of my own personal firsthand knowledge. I make this declaration in support of Immunex's Motion for Summary Adjudication of Infringement Under 35 U.S.C. § 271(e)(2)(C).

2. Attached hereto as **Exhibit A** is a true and correct copy of a document produced by the defendants in this action bearing production numbers SAN-ETAN_0000827 – 29.

3. Exhibit A is the cover letter from Sandoz Inc. to the FDA for BLA 761042 as originally submitted on July 30, 2015.

4. Exhibit A stated on pages 1 to 3, in part:

5. The defendants produced Exhibit A before October 12, 2016 with the legend "HIGHLY CONFIDENTIAL." Pursuant to Paragraph 3 of the Stipulated Amended Discovery Confidentiality Order (Dkt. No. 124) (hereinafter "Amended DCO"), Exhibit A is now designated "CONFIDENTIAL."

6. Attached hereto as **Exhibit B** is a true and correct copy of a document produced by the defendants in this action bearing production numbers SAN-ETAN_0000184-86.

7. Exhibit B is the BLA Form FDA 356h as originally submitted as part of BLA 761042.

8. Page 1, cell 15 of Exhibit B

9. Page 1, cell 19 of Exhibit B [redacted]

10. Page 2, cell 25 of Exhibit B [redacted]

11. The defendants produced Exhibit B before October 12, 2016 with the legend "HIGHLY CONFIDENTIAL." Pursuant to Paragraph 3 of the Amended DCO, Exhibit B is now designated "CONFIDENTIAL."

12. Attached hereto as **Exhibit C** is a true and correct copy of a document produced by the defendants in this action bearing production numbers SAN-ETAN_0000624 – 64.

13. Exhibit C is [redacted]

14. In Exhibit C, [redacted]

[redacted]

[redacted]

Ex. C at SAN-ETAN_0000624

[redacted]

Ex. C at SAN-ETAN_0000626.

[redacted]

Ex. C at SAN-ETAN_0000626.

15. Exhibit C [redacted]

Ex. C at SAN-ETAN_0000626.

Ex. C at SAN-ETAN_0000624.

16. The defendants produced Exhibit C before October 12, 2016 with the legend "HIGHLY CONFIDENTIAL." Pursuant to Paragraph 3 of the Amended DCO, Exhibit C is now designated "CONFIDENTIAL."

17. Attached hereto as **Exhibit D** is a true and correct copy of a document produced by Immunex in this action bearing production numbers AMG-ENBNJ-00353756 – 808. Exhibit D is the FDA-approved label for Sandoz's etanercept biological product taken from the FDA's website at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761042lbl.pdf.

18. Attached hereto as **Exhibit E** is a true and correct copy of a letter from Maureen Rurka to Peter Choi and Aaron Maurer dated July 27, 2017. The first paragraph of Exhibit E reads, in part, [redacted]

19. Attached hereto as **Exhibit F** is a true and correct copy of Immunex's letter sent pursuant to 26 U.S.C. § 262(*l*)(3)(A) on December 18, 2015. In this letter, Immunex lists the '631 patent as a patent which Immunex believed could reasonably be asserted against Sandoz.

20. The first page of Exhibit F states that it "Contains information designated 'HIGHLY CONFIDENTIAL' by Sandoz Inc." Pursuant to Paragraph 24 of the Amended DCO, Exhibit F, which was designated pursuant to the parties' October 26, 2015 Confidentiality Agreement, is now designated "CONFIDENTIAL."

21. Defendant Sandoz Inc.'s Invalidity and Noninfringement Contentions, dated July 29, 2016, are 285 pages long, not including associated charts. Attached

hereto as **Exhibit G** is a true and correct copy of excerpts from Defendant Sandoz Inc.'s Invalidity and Noninfringement Contentions in this action, specifically, pages 1, 283, 284, and 285.

22. Attached hereto as **Exhibit H** is a true and correct copy of Exhibit N to Defendant Sandoz Inc.'s Invalidity and Noninfringement Contentions in this action.

[redacted]

23. Attached hereto as **Exhibit I** is a true and correct copy of the Joint Claim Construction and Prehearing Statement Pursuant to L. Pat. R. 4.3 submitted in this action on October 17, 2016.

24. On page 2 of Exhibit I, the parties agreed to constructions of claim terms in the Immunex Patents whereby "TNFR:Fc" meant "etanercept" (highlighting added):

Term / Claims	Asserted Claims	Agreed Construction
"therapeutically effective dose"	'225 claims 1-9, 12-15 '605 claims 1-4, 10-13	Plain and ordinary meaning: "an amount suitable for therapy"
"wherein (a) a dose of 50 mg of TNFR:Fc is administered two times per week for at least two months and then (b) TNFR:Fc is administered at a reduced dose or a reduced frequency"	'225 claims 5-8 '605 claims 10-13	Plain and ordinary meaning: "wherein (a) a dose of 50 mg of etanercept is administered two times per week for at least two months and then (b) etanercept is administered at a reduced dose or at a reduced frequency"
"(a) administering to the patient TNFR:Fc subcutaneously at a dose of 50 mg twice per week for at least two months, and then (b) administering TNFR:Fc subcutaneously at a dose of 50 mg once per week or at a dose of 25 mg twice per week"	'225 claims 16, 20	Plain and ordinary meaning: "(a) administering to the patient etanercept subcutaneously at a dose of 50 mg twice per week for at least two months, and then (b) administering etanercept subcutaneously at a dose of 50 mg once per week or at a dose of 25 mg twice per week"

25. According to page SAN-ETAN_0000634 of Exhibit C, [redacted]

26. On November 3, 2016, the parties agreed that Exhibit I could be filed publicly. *See* Dkt. No. 126.

27. Attached hereto as **Exhibit J** is a true and correct copy of a letter from Maureen L. Rurka on behalf of Sandoz to Jeffrey P. Kushan dated July 10, 2016.

28. In Exhibit J, Ms. Rurka stated "Sandoz has filed an application for FDA approval of a Sandoz biosimilar etanercept product, for which Immunex's ENBREL® is the reference product. Sandoz . . . expects . . . to receive FDA approval to market its product on August 30, 2016. Absent some agreement between the parties, Sandoz intends to begin commercial marketing of its product immediately thereafter."

29. Immunex Corporation holds the BLA for Enbrel®. Ex. J at 1.

30. Attached hereto as **Exhibit K** is a true and correct copy of U.S. Patent No. 8,722,631 ("the '631 Patent"). Claim 1 of U.S. Patent No. 8,722,631 recites "A method of treatment comprising administering a dose of TNFR:Fc to a patient having psoriatic arthritis and/or plaque psoriasis, wherein the dose is administered one time or two times per week, and wherein the dose administered is 25-50 mg or 50-100 mg, and wherein the dose is administered by subcutaneous injection."

31. Attached hereto as **Exhibit L** is a true and correct copy of a document produced by the defendants in this action bearing production numbers SAN-ETAN_0188099 – 171. Exhibit L is a [redacted]. The defendants produced Exhibit L before October 12, 2016 with the legend "HIGHLY CONFIDENTIAL – OUTSIDE COUNSEL'S EYES ONLY." Pursuant to Paragraph 3 of the Amended DCO, Exhibit L is now designated "CONFIDENTIAL."

32. Attached hereto as **Exhibit M** is a true and correct copy of a document included as A1556-57 in the Joint Appendix from an appeal in prior litigation, *Sandoz Inc. v. Amgen Inc*., 773 F.3d 1274 (Fed. Cir. 2014). Exhibit M is a letter from Sandoz Inc. to Amgen Inc. and Hoffman-La Roche, Inc. dated June 14, 2013 which on page A1556 states "Sandoz Inc., has developed an etanercept product, biosimilar to Enbrel®, which they intend to market in the United States following necessary regulatory approvals."

33. Attached hereto as **Exhibit N** is a true and correct copy of a document produced by the defendants in this action bearing production numbers SAN-ETAN_0346012 – 49. The first page of Exhibit N, page SAN-ETAN_0346012, [redacted]

34. Page SAN-ETAN_0346014 of Exhibit N [redacted]

35. Page SAN-ETAN_0346043 of Exhibit N states [redacted]

I declare under oath pursuant to 28 U.S.C. § 1746 that the above is true and correct and that the above is executed in Burlingame, California on September 12, 2017.

Dated: September 12, 2017

James A. High Jr.

EXHBIT A
REDACTED
IN FULL

EXHBIT B
REDACTED
IN FULL

EXHBIT C
REDACTED
IN FULL

EXHBIT D

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ERELZI™ safely and effectively. See full prescribing information for ERELZI.

ERELZI (etanercept-szzs) injection, for subcutaneous use

Initial U.S. Approval: 2016

ERELZI (etanercept-szzs) is biosimilar to ENBREL® (etanercept).*

WARNINGS:

SERIOUS INFECTIONS AND MALIGNANCIES

See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal iufections (such as histoplasmosis), and infections due to other opportunistic pathogens. (5.1)**
- **ERELZI should be discontinued if a patient develops a serious infection or sepsis during treatment. (5.1)**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting ERELZI. (5.1)**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

MALIGNANCIES

- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including etanercept products. (5.3)**

----------**INDICATIONS AND USAGE**----------

ERELZI is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- Rheumatoid Arthritis (RA) (1.1)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older (1.2)
- Psoriatic Arthritis (PsA) (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Plaque Psoriasis (PsO) (1.5)

----------**DOSAGE AND ADMINISTRATION**--------

ERELZI is administered by subcutaneous injection.

- Adult RA and PsA (2.1)
  50 mg once weekly with or without methotrexate (MTX)
- AS (2.1)
  50 mg once weekly
- Adult PsO (2.2)
  50 mg twice weekly for 3 months, followed by 50 mg once weekly
- JIA (patients who weigh >63 kg) (2.3)
  0.8 mg/kg weekly, with a maximum of 50 mg per week

----------**DOSAGE FORMS AND STRENGTHS**--------

- Injection: 25 mg/0.5 mL and 50 mg/mL solution in a single-dose prefilled syringe with BD UltraSafe Passive® Needle Guard (3)
- Injection: 50 mg/mL solution in single-dose prefilled Sensoready® Pen (3)

----------**CONTRAINDICATIONS**----------

- Sepsis (4)

----------**WARNINGS AND PRECAUTIONS**--------

- Do not start ERELZI during an active infection. If an infection develops, monitor carefully and stop ERELZI if infection becomes serious. (5.1)
- Consider empiric anti-fungal therapy for patients at risk for invasive fungal infections who develop a severe systemic illness on ERELZI (those who reside or travel to regions where mycoses are endemic). (5.1)
- Demyelinating disease, exacerbation or new onset, may occur. (5.2)
- Cases of lymphoma have been observed in patients receiving TNF-blocking agents. (5.3)
- Congestive heart failure, worsening or new onset, may occur. (5.4)
- Advise patients to seek immediate medical attention if symptoms of pancytopenia or aplastic anemia develop, and consider stopping ERELZI. (5.5)
- Monitor patients previously infected with hepatitis B virus for reactivation during and several months after therapy. If reactivation occurs, consider stopping ERELZI and beginning anti-viral therapy. (5.6)
- Anaphylaxis or serious allergic reactions may occur. (5.7)
- Stop ERELZI if lupus-like syndrome or autoimmune hepatitis develops. (5.9)

----------**ADVERSE REACTIONS**----------

Most common adverse reactions (incidence > 5%): infections and injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------**DRUG INTERACTIONS**----------

- Live vaccines – should not be given with ERELZI (5.8, 7.1)
- Anakinra – increased risk of serious infection (5.12, 7.2)
- Abatacept – increased risk of serious adverse events, including infections (5.12, 7.2)

- Cyclophosphamide – use with ERELZI is not recommended (7.3)

* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of Erelzi has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 08/2016

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNINGS: SERIOUS INFECTIONS AND MALIGNANCIES

SERIOUS INFECTIONS

Patients treated with etanercept products are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and Adverse Reactions (6)]*. Most patients treated with etanercept products who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

ERELZI should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before ERELZI use and during therapy. Treatment for latent infection should be initiated prior to ERELZI use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with ERELZI should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ERELZI, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCIES

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including etanercept products.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

ERELZI is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA). ERELZI can be initiated in combination with methotrexate (MTX) or used alone.

1.2 Polyarticular Juvenile Idiopathic Arthritis

ERELZI is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 and older.

1.3 Psoriatic Arthritis

ERELZI is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA). ERELZI can be used in combination with methotrexate (MTX) in patients who do not respond adequately to MTX alone.

1.4 Ankylosing Spondylitis

ERELZI is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis (AS).

1.5 Plaque Psoriasis

ERELZI is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

2 DOSAGE AND ADMINISTRATION

ERELZI is administered by subcutaneous injection.

Table 1. Dosing and Administration for Adult Patients

Patient Population	Recommended Dosage Strength and Frequency
Adult RA, AS, and PsA Patients	50 mg weekly
Adult PsO Patients	Starting Dose: 50 mg twice weekly for 3 months Maintenance Dose: 50 mg once weekly

See the ERELZI (etanercept-szzs) "Instructions for Use" insert for detailed information on injection site selection and dose administration. *[see Dosage and Administration (2.4) and Patient Counseling Information (17.2)]*

2.1 Adult Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Patients

MTX, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ERELZI.

Based on a study of 50 mg etanercept twice weekly in patients with RA that suggested higher incidence of adverse reactions but similar American College of Rheumatology (ACR) response rates, doses higher than 50 mg per week are not recommended.

2.2 Adult Plaque Psoriasis Patients

In addition to the 50 mg twice weekly recommended starting dose, starting doses of 25 mg or 50 mg per week were shown to be efficacious. The proportion of responders was related to etanercept dosage *[see Clinical Studies (14.5)]*.

2.3 JIA Patients

Table 2. Dosing and Administration for Juvenile Idiopathic Arthritis

Pediatric Patients Weight	**Recommended Dose**
63 kg (138 pounds) or more	50 mg weekly

Note: There is no dosage form for ERELZI that allows weight based dosing for pediatric patients below 63 kg.

In JIA patients, glucocorticoids, NSAIDs, or analgesics may be continued during treatment with ERELZI. Higher doses of etanercept products have not been studied in pediatric patients.

2.4 Preparation of ERELZI

ERELZI is intended for use under the guidance and supervision of a physician. Patients may self-inject when deemed appropriate and if they receive medical follow-up, as necessary. Patients should not self-administer until they receive proper training in how to prepare and administer the correct dose. Injections should occur in the thigh, abdomen, or outer area of the upper arm.

The ERELZI (etanercept-szzs) "Instructions for Use" insert for each presentation contains more detailed instructions on the preparation of ERELZI.

Preparation of ERELZI Using the Single-dose Prefilled Syringe or Single-dose Prefilled Sensoready Pen

Leave ERELZI at room temperature for about 15 to 30 minutes before injecting. DO NOT remove the needle cover while allowing the prefilled syringe to reach room temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. There may be small white particles of protein in the solution. This is not unusual for proteinaceous solutions. The solution should not be used if discolored or cloudy, or if foreign particulate matter is present.

2.5 Monitoring to Assess Safety

Prior to initiating ERELZI and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

ERELZI is a clear and colorless to slightly yellow solution available as:

Injection: 25 mg/0.5 mL and 50 mg/mL solution in a single-dose prefilled syringe with BD UltraSafe Passive™ Needle Guard

Injection: 50 mg/mL solution in a single-dose prefilled Sensoready® Pen

4 CONTRAINDICATIONS

ERELZI should not be administered to patients with sepsis.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with ERELZI are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with ERELZI should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- With chronic or recurrent infection;
- Who have been exposed to tuberculosis;
- With a history of an opportunistic infection;
- Who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- With underlying conditions that may predispose them to infection, such as advanced or poorly controlled diabetes *[see Adverse Reactions (6.1)]*.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ERELZI.

ERELZI should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with ERELZI should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving etanercept products, including patients who have previously received treatment for latent or active tuberculosis. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with etanercept products than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including etanercept products. Tuberculosis has developed in patients who tested negative for latent tuberculosis prior to initiation of therapy. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ERELZI and periodically during therapy. Tests for latent tuberculosis infection may be falsely negative while on therapy with ERELZI.

Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating ERELZI, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of ERELZI in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Tuberculosis should be strongly considered in patients who develop a new infection during ERELZI treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Invasive Fungal Infections

Cases of serious and sometimes fatal fungal infections, including histoplasmosis, have been reported with TNF blockers, including etanercept products. For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric anti-fungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric anti-fungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of anti-fungal therapy. In 38 of etanercept's clinical trials and 4 cohort studies in all approved indications representing 27,169 patient-years of exposure (17,696 patients) from the United States and Canada, no histoplasmosis infections were reported among patients treated with etanercept products.

5.2 Neurologic Events

Treatment with TNF-blocking agents, including etanercept products, has been associated with rare (< 0.1%) cases of new onset or exacerbation of central nervous system demyelinating

disorders, some presenting with mental status changes and some associated with permanent disability, and with peripheral nervous system demyelinating disorders. Cases of transverse myelitis, optic neuritis, multiple sclerosis, Guillain-Barré syndromes, other peripheral demyelinating neuropathies, and new onset or exacerbation of seizure disorders have been reported in postmarketing experience with etanercept products therapy. Prescribers should exercise caution in considering the use of ERELZI in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders *[see Adverse Reactions (6.2)]*.

5.3 Malignancies

Lymphomas

In the controlled portions of clinical trials of TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared to control patients. During the controlled portions of etanercept's trials in adult patients with RA, AS, and PsA, 2 lymphomas were observed among 3306 etanercept-treated patients versus 0 among 1521 control patients (duration of controlled treatment ranged from 3 to 36 months).

Among 6543 adult rheumatology (RA, PsA, AS) patients treated with etanercept in controlled and uncontrolled portions of clinical trials, representing approximately 12,845 patient-years of therapy, the observed rate of lymphoma was 0.10 cases per 100 patient-years. This was 3-fold higher than the rate of lymphoma expected in the general U.S. population based on the Surveillance, Epidemiology, and End Results (SEER) Database. An increased rate of lymphoma up to several-fold has been reported in the RA patient population, and may be further increased in patients with more severe disease activity.

Among 4410 adult PsO patients treated with etanercept in clinical trials up to 36 months, representing approximately 4278 patient-years of therapy, the observed rate of lymphoma was 0.05 cases per 100 patient-years, which is comparable to the rate in the general population. No cases were observed in etanercept- or placebo-treated patients during the controlled portions of these trials.

Leukemia

Cases of acute and chronic leukemia have been reported in association with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at higher risk (approximately 2-fold) than the general population for the development of leukemia.

During the controlled portions of etanercept's trials, 2 cases of leukemia were observed among 5445 (0.06 cases per 100 patient-years) etanercept-treated patients versus 0 among 2890 (0%) control patients (duration of controlled treatment ranged from 3 to 48 months).

Among 15,401 patients treated with etanercept in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of leukemia was 0.03 cases per 100 patient-years.

Other Malignancies

Information is available from 10,953 adult patients with 17,123 patient-years and 696 pediatric patients with 1282 patient-years of experience across 45 etanercept clinical studies.

For malignancies other than lymphoma and non-melanoma skin cancer, there was no difference in exposure adjusted rates between etanercept and control arms in the controlled portions of clinical studies for all indications. Analysis of the malignancy rate in combined controlled and uncontrolled portions of studies has demonstrated that types and rates are similar to what is expected in the general U.S. population based on the SEER database and suggests no increase in rates over time. Whether treatment with etanercept products might influence the development and course of malignancies in adults is unknown.

Melanoma and Non-melanoma skin cancer (NMSC)

Melanoma and non-melanoma skin cancer has been reported in patients treated with TNF antagonists including etanercept products.

Among 15,401 patients treated with etanercept in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of melanoma was 0.043 cases per 100 patient-years.

Among 3306 adult rheumatology (RA, PsA, AS) patients treated with etanercept in controlled clinical trials representing approximately 2669 patient-years of therapy, the observed rate of NMSC was 0.41 cases per 100 patient-years vs 0.37 cases per 100 patient-years among 1521 control-treated patients representing 1077 patient-years. Among 1245 adult psoriasis patients treated with etanercept in controlled clinical trials, representing approximately 283 patient-years of therapy, the observed rate of NMSC was 3.54 cases per 100 patient-years vs 1.28 cases per 100 patient-years among 720 control-treated patients representing 156 patient-years.

Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept products.

Periodic skin examinations should be considered for all patients at increased risk for skin cancer.

Pediatric Patients

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy at ≤ 18 years of age), including etanercept products. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

In clinical trials of 1140 pediatric patients representing 1927.2 patient-years of therapy, no malignancies, including lymphoma or NMSC, have been reported.

Postmarketing Use

In global postmarketing adult and pediatric use, lymphoma and other malignancies have been reported.

5.4 Patients With Heart Failure

Two clinical trials evaluating the use of etanercept in the treatment of heart failure were terminated early due to lack of efficacy. One of these studies suggested higher mortality in etanercept-treated patients compared to placebo *[see Adverse Reactions (6.2)]*. There have been postmarketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking etanercept products. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known preexisting cardiovascular disease. Some of these patients have been under 50 years of age. Physicians should exercise caution when using ERELZI in patients who also have heart failure, and monitor patients carefully.

5.5 Hematologic Events

Rare (< 0.1%) reports of pancytopenia, including very rare (< 0.01%) reports of aplastic anemia, some with a fatal outcome, have been reported in patients treated with etanercept. The causal relationship to therapy with etanercept products remains unclear. Although no high-risk group has been identified, caution should be exercised in patients being treated with ERELZI who have a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ERELZI. Discontinuation of ERELZI therapy should be considered in patients with confirmed significant hematologic abnormalities.

Two percent of patients treated concurrently with etanercept and anakinra developed neutropenia (ANC < 1 x 10^9 /L). While neutropenic, one patient developed cellulitis that resolved with antibiotic therapy.

5.6 Hepatitis B Reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-blocking agents, including very rare cases (< 0.01%) with etanercept, has been reported. In some instances, hepatitis B reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to hepatitis B reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. Prescribers should exercise caution in prescribing TNF blockers in patients previously infected with HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients previously infected with HBV and require treatment with ERELZI should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, consideration should be given to stopping ERELZI and initiating anti-viral therapy with appropriate supportive treatment. The safety of resuming therapy with etanercept products after HBV reactivation is controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

5.7 Allergic Reactions

Allergic reactions associated with administration of etanercept during clinical trials have been reported in < 2% of patients. If an anaphylactic reaction or other serious allergic reaction occurs, administration of ERELZI should be discontinued immediately and appropriate therapy initiated.

Caution: The following components contain dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex: the needle cap of the prefilled syringe and the internal needle cover within the cap of the Sensoready Pen.

5.8 Immunizations

Live vaccines should not be given concurrently with ERELZI. It is recommended that pediatric patients, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating ERELZI therapy *[see Drug Interactions (7.1)]*.

5.9 Autoimmunity

Treatment with ERELZI may result in the formation of autoantibodies *[see Adverse Reactions (6.1)]* and, rarely (< 0.1%), in the development of a lupus-like syndrome or autoimmune hepatitis *[see Adverse Reactions (6.2)]*, which may resolve following withdrawal of ERELZI. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with ERELZI, treatment should be discontinued and the patient should be carefully evaluated.

5.10 Immunosuppression

TNF mediates inflammation and modulates cellular immune responses. TNF-blocking agents, including ERELZI, affect host defenses against infections. The effect of TNF inhibition on the development and course of malignancies is not fully understood. In a study of 49 patients with RA treated with etanercept, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations *[see Warnings and Precautions (5.1, 5.3) and Adverse Reactions (6.1)]*.

5.11 Use in Wegener's Granulomatosis Patients

The use of ERELZI in patients with Wegener's granulomatosis receiving immunosuppressive agents is not recommended. In a study of patients with Wegener's granulomatosis, the addition of etanercept to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies and was not associated with improved clinical outcomes when compared with standard therapy alone *[see Drug Interactions (7.3)]*.

5.12 Use with Anakinra or Abatacept

Use of ERELZI with anakinra or abatacept is not recommended *[see Drug Interactions (7.2)]*.

5.13 Use in Patients with Moderate to Severe Alcoholic Hepatitis

In a study of 48 hospitalized patients treated with etanercept or placebo for moderate to severe alcoholic hepatitis, the mortality rate in patients treated with etanercept was similar to patients treated with placebo at 1 month but significantly higher after 6 months. Physicians should use caution when using ERELZI in patients with moderate to severe alcoholic hepatitis.

6 ADVERSE REACTIONS

Across clinical studies and postmarketing experience, the most serious adverse reactions with etanercept were infections, neurologic events, CHF, and hematologic events *[see Warnings and Precautions (5)]*. The most common adverse reactions with etanercept were infections and injection site reactions.

6.1 Clinical Studies Experience

Adverse Reactions in Adult Patients with Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, or Plaque Psoriasis

The data described below reflect exposure to etanercept in 2219 adult patients with RA followed for up to 80 months, in 182 patients with PsA for up to 24 months, in 138 patients with AS for up to 6 months, and in 1204 adult patients with PsO for up to 18 months.

In controlled trials, the proportion of etanercept-treated patients who discontinued treatment due to adverse events was approximately 4% in the indications studied.

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in clinical practice.

Infections

Infections, including viral, bacterial, and fungal infections, have been observed in adult and pediatric patients. Infections have been noted in all body systems and have been reported in patients receiving etanercept products alone or in combination with other immunosuppressive agents.

In controlled portions of trials, the types and severity of infection were similar between etanercept and the respective control group (placebo or MTX for RA and PsA patients) in RA, PsA, AS and PsO patients. Rates of infections in RA and PsO patients are provided in Table 3 and Table 4, respectively. Infections consisted primarily of upper respiratory tract infection, sinusitis and influenza.

In controlled portions of trials in RA, PsA, AS and PsO, the rates of serious infection were similar (0.8% in placebo, 3.6% in MTX, and 1.4% in etanercept/etanercept + MTX-treated groups). In clinical trials in rheumatologic indications, serious infections experienced by patients have included, but are not limited to, pneumonia, cellulitis, septic arthritis, bronchitis, gastroenteritis, pyelonephritis, sepsis, abscess and osteomyelitis. In clinical trials in PsO, serious infections experienced by patients have included, but are not limited to, pneumonia, cellulitis, gastroenteritis, abscess and osteomyelitis. The rate of serious infections was not increased in

open-label extension trials and was similar to that observed in etanercept- and placebo-treated patients from controlled trials.

In 66 global clinical trials of 17,505 patients (21,015 patient-years of therapy), tuberculosis was observed in approximately 0.02% of patients. In 17,696 patients (27,169 patient-years of therapy) from 38 clinical trials and 4 cohort studies in the U.S. and Canada, tuberculosis was observed in approximately 0.006% of patients. These studies include reports of pulmonary and extrapulmonary tuberculosis *[see Warnings and Precautions (5.1)]*.

Injection Site Reactions

In placebo-controlled trials in rheumatologic indications, approximately 37% of patients treated with etanercept developed injection site reactions. In controlled trials in patients with PsO, 15% of patients treated with etanercept developed injection site reactions during the first 3 months of treatment. All injection site reactions were described as mild to moderate (erythema, itching, pain, swelling, bleeding, bruising) and generally did not necessitate drug discontinuation. Injection site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness at a previous injection site when subsequent injections were given.

Immunogenicity

Patients with RA, PsA, AS or PsO were tested at multiple time points for antibodies to etanercept. Antibodies to the TNF receptor portion or other protein components of etanercept were detected at least once in sera of approximately 6% of adult patients with RA, PsA, AS or PsO. These antibodies were all non-neutralizing. Results from JIA patients were similar to those seen in adult RA patients treated with etanercept.

In PsO studies that evaluated the exposure of etanercept for up to 120 weeks, the percentage of patients testing positive at the assessed time points of 24, 48, 72 and 96 weeks ranged from 3.6%-8.7% and were all non-neutralizing. The percentage of patients testing positive increased with an increase in the duration of study; however, the clinical significance of this finding is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The immunogenicity data of etanercept beyond 120 weeks of exposure are unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to etanercept in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of any antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to etanercept reported in this section with the incidence of antibodies in other studies or to other products may be misleading.

Autoantibodies

Patients with RA had serum samples tested for autoantibodies at multiple time points. In RA Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA) who

developed new positive ANA (titer ≥ 1:40) was higher in patients treated with etanercept (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with etanercept compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with etanercept compared to none of placebo-treated patients). The proportion of patients treated with etanercept who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. In RA Study III, no pattern of increased autoantibody development was seen in etanercept's patients compared to MTX patients *[see Warnings and Precautions (5.9)]*.

Other Adverse Reactions

Table 3 summarizes adverse reactions reported in adult RA patients. The types of adverse reactions seen in patients with PsA or AS were similar to the types of adverse reactions seen in patients with RA.

Table 3. Percent of Adult RA Patients Experiencing Adverse Reactions in Controlled Clinical Trials

	Placebo Controlled[a] (Studies I, II and a Phase 2 Study)		**Active Controlled[b] (Study III)**	
	Placebo (N= 152)	**Etanercept[c] (N= 349)**	**MTX (N= 217)**	**Etanercept[c] (N= 415)**
Reaction	**Percent of Patients**		**Percent of Patients**	
Infection[d] (total)	39	50	86	81
Upper Respiratory Infections[e]	30	38	70	65
Non-upper Respiratory Infections	15	21	59	54
Injection Site Reactions	11	37	18	43
Diarrhea	9	8	16	16
Rash	2	3	19	13
Pruritus	1	2	5	5
Pyrexia	-	3	4	2
Urticaria	1	-	4	2

Hypersensitivity	-	-	1	1

[a]Includes data from the 6-month study in which patients received concurrent MTX therapy in both arms.
[b]Study duration of 2 years.
[c]Any dose.
[d]Includes bacterial, viral and fungal infections.
[e]Most frequent Upper Respiratory Infections were upper respiratory tract infection, sinusitis, and influenza.

In placebo-controlled PsO trials, the percentages of patients reporting adverse reactions in the 50 mg twice a week dose group were similar to those observed in the 25 mg twice a week dose group or placebo group.

Table 4 summarizes adverse reactions reported in adult PsO patients from Studies I and II.

Table 4. Percent of Adult PsO Patients Experiencing Adverse Reactions in Placebo-Controlled Portions of Clinical Trials (Studies I & II)

	Placebo (N= 359)	**Etanercept[a] (N= 876)**
Reaction	**Percent of Patients**	
Infection[b] (total)	28	27
Non-upper Respiratory Infections	14	12
Upper Respiratory Infections[c]	17	17
Injection Site Reactions	6	15
Diarrhea	2	3
Rash	1	1
Pruritus	2	1
Urticaria	-	1
Hypersensitivity	-	1
Pyrexia	1	-

[a]Includes 25 mg subcutaneous (SC) once weekly (QW), 25 mg SC twice weekly (BIW), 50 mg SC QW, and 50 mg SC BIW doses.
[b]Includes bacterial, viral and fungal infections.
[c]Most frequent Upper Respiratory Infections were upper respiratory tract infection, nasopharyngitis, and sinusitis.

Adverse Reactions in Pediatric Patients

In general, the adverse reactions in pediatric patients were similar in frequency and type as those seen in adult patients *[see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Studies (14.2)]*. The types of infections reported in pediatric patients were generally mild and consistent with those commonly seen in the general pediatric population. Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae.

In open-label clinical studies of children with JIA, adverse reactions reported in those ages 2 to 4 years were similar to adverse reactions reported in older children.

6.2 Postmarketing Experience

Adverse reactions have been reported during post approval use of etanercept in adults and pediatric patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to etanercept exposure.

Adverse reactions are listed by body system below:

Blood and lymphatic system disorders:	pancytopenia, anemia, leukopenia, neutropenia, thrombocytopenia, lymphadenopathy, aplastic anemia *[see Warnings and Precautions (5.5)]*
Cardiac disorders:	congestive heart failure *[see Warnings and Precautions (5.4)]*
Gastrointestinal disorders:	inflammatory bowel disease (IBD)
General disorders:	angioedema, chest pain
Hepatobiliary disorders:	autoimmune hepatitis, elevated transaminases, hepatitis B reactivation
Immune disorders:	macrophage activation syndrome, systemic vasculitis, sarcoidosis
Musculoskeletal and connective tissue disorders:	lupus-like syndrome
Neoplasms benign, malignant, and unspecified:	melanoma and non-melanoma skin cancers, Merkel cell carcinoma *[see Warnings and Precautions (5.3)]*
Nervous system disorders:	convulsions, multiple sclerosis, demyelination, optic neuritis, transverse myelitis, paresthesias *[see Warnings and Precautions (5.2)]*
Ocular disorders:	uveitis, scleritis
Respiratory, thoracic and mediastinal disorders:	interstitial lung disease
Skin and subcutaneous tissue disorders:	cutaneous lupus erythematosus, cutaneous vasculitis (including leukocytoclastic vasculitis), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, subcutaneous nodule, new or worsening psoriasis (all sub-types including pustular and palmoplantar)

Opportunistic infections, including atypical mycobacterial infection, herpes zoster, aspergillosis and *Pneumocystis jiroveci* pneumonia, and protozoal infections have also been reported in postmarketing use.

7 DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with etanercept products.

7.1 Vaccines

Most PsA patients receiving etanercept were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had 2-fold rises in titers compared to patients not receiving etanercept. The clinical significance of this is unknown. Patients receiving ERELZI may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving etanercept products.

Patients with a significant exposure to varicella virus should temporarily discontinue ERELZI therapy and be considered for prophylactic treatment with varicella zoster immune globulin *[see Warnings and Precautions (5.8, 5.10)]*.

7.2 Immune-Modulating Biologic Products

In a study in which patients with active RA were treated for up to 24 weeks concurrently with etanercept and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with etanercept alone (0%) [*see Warnings and Precautions (5.12)*] and did not result in higher ACR response rates compared to etanercept alone. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure. Two percent of patients treated concurrently with etanercept and anakinra developed neutropenia (ANC $< 1 \times 10^9$/L).

In clinical studies, concurrent administration of abatacept and etanercept resulted in increased incidences of serious adverse events, including infections, and did not demonstrate increased clinical benefit *[see Warnings and Precautions (5.12)]*.

7.3 Cyclophosphamide

The use of ERELZI in patients receiving concurrent cyclophosphamide therapy is not recommended *[see Warnings and Precautions (5.11)]*.

7.4 Sulfasalazine

Patients in a clinical study who were on established therapy with sulfasalazine, to which etanercept was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either etanercept or sulfasalazine alone. The clinical significance of this observation is unknown.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on use of etanercept in pregnant women are insufficient to inform a drug-associated risk. Published studies with etanercept use during pregnancy have not reported a clear association with etanercept and major birth defect or miscarriage risk. Based on limited data, etanercept concentration in cord blood at the time of delivery showed that etanercept crossed the placenta in small amounts *[see Clinical Considerations]*. Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept *[see Data]*. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Etanercept crosses the placenta in small amounts *[see Data]*. The clinical significance of infant exposure to etanercept products *in utero* is unknown.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with etanercept and major birth defects, miscarriage, or adverse maternal or fetal outcomes when etanercept was used during pregnancy. However, these studies cannot definitely establish the absence of any etanercept-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Three case reports showed that cord blood levels of etanercept at delivery in infants, born to mothers administered etanercept during pregnancy, were between 3 and 32% of the maternal serum level.

Animal Data

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept.

8.2 Lactation

Risk Summary

Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. There are no data on the effects on the breastfed infant, or the effects on milk production. The limited clinical data during lactation precludes a clear determination of the risk of etanercept products to an infant during lactation; therefore, developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ERELZI and any potential adverse effects on the breastfed child from ERELZI or from the underlying maternal condition.

8.4 Pediatric Use

Etanercept has not been studied in children < 2 years of age with JIA. The safety and efficacy of etanercept in pediatric patients with PsO have not been established.

Rare (< 0.1%) cases of IBD have been reported in JIA patients receiving etanercept, which is not effective for the treatment of IBD *[see Adverse Reactions (6.2)]*.

The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to exposed infants.

8.5 Geriatric Use

A total of 480 RA patients ages 65 years or older have been studied in clinical trials. In PsO randomized clinical trials, a total of 138 out of 1965 patients treated with etanercept or placebo were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but the number of geriatric PsO patients is too small to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

8.6 Use in Diabetics

There have been reports of hypoglycemia following initiation of etanercept in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

10 OVERDOSAGE

Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of etanercept. Single IV doses up to 60 mg/m^2 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

11 DESCRIPTION

ERELZI (etanercept-szzs) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept-szzs contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. Etanercept-szzs is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

The solution of ERELZI (etanercept-szzs) Injection in the single-dose prefilled syringe with BD UltraSafe Passive Needle Guard and the single-dose prefilled Sensoready Pen is clear and colorless to slightly yellow, sterile, preservative-free, and is formulated at pH 6.3 ± 0.2. ERELZI is for subcutaneous use.

Table 5. Contents of ERELZI

Presentation	Active Ingredient Content	Inactive Ingredients Content
Etanercept-szzs 50 mg prefilled syringe with BD UltraSafe Passive Needle Guard and Sensoready Pen	50 mg etanercept-szzs in 1 mL	0.786 mg citric acid 13.52 mg sodium citrate 1.5 mg sodium chloride 10 mg sucrose 4.6 mg lysine
Etanercept-szzs 25 mg prefilled syringe with BD UltraSafe Passive Needle Guard	25 mg etanercept-szzs in 0.5 mL	0.393 mg citric acid 6.76 mg sodium citrate 0.75 mg sodium chloride 5 mg sucrose 2.3 mg lysine

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of RA, polyarticular JIA, PsA, and AS and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PsA, AS, and PsO.

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept products are dimeric soluble forms of the p75 TNF receptor that can bind TNF molecules. Etanercept products inhibit binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNFRs, rendering TNF biologically inactive. In *in vitro* studies, large complexes of etanercept with TNF-α were not detected and cells expressing transmembrane TNF (that binds etanercept products) are not lysed in the presence or absence of complement.

12.2 Pharmacodynamics

Etanercept products can modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (eg, E-selectin, and to a lesser extent, intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (eg, IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin). Etanercept products have been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.

12.3 Pharmacokinetics

After administration of 25 mg of etanercept by a single SC injection to 25 patients with RA, a mean ± standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (C_{max}) of 1.1 ± 0.6 mcg/mL and time to C_{max} of 69 ± 34 hours was observed in these patients following a single 25 mg dose. After 6 months of twice weekly 25 mg doses in these same RA patients, the mean C_{max} was 2.4 ± 1.0 mcg/mL (N = 23). Patients exhibited a 2- to 7-fold increase in peak serum concentrations and approximately 4-fold increase in $AUC_{0\text{-}72\ hr}$ (range 1- to 17-fold) with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months. The pharmacokinetic parameters in patients with PsO were similar to those seen in patients with RA.

In another study, serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg etanercept once weekly and those treated with 25 mg etanercept twice weekly. The mean (± standard deviation) C_{max}, C_{min}, and partial AUC were 2.4 ± 1.5 mcg/mL, 1.2 ± 0.7 mcg/mL, and 297 ± 166 mcg•h/mL, respectively, for patients treated with 50 mg etanercept once weekly (N = 21); and 2.6 ± 1.2 mcg/mL, 1.4 ± 0.7 mcg/mL, and 316 ± 135 mcg•h/mL for patients treated with 25 mg etanercept twice weekly (N = 16).

Patients with JIA (ages 4 to 17 years) were administered 0.4 mg/kg of etanercept twice weekly (up to a maximum dose of 50 mg per week) for up to 18 weeks. The mean serum concentration after repeated SC dosing was 2.1 mcg/mL, with a range of 0.7 to 4.3 mcg/mL. Limited data suggest that the clearance of etanercept is reduced slightly in children ages 4 to 8 years. Population pharmacokinetic analyses predict that the pharmacokinetic differences between the regimens of 0.4 mg/kg twice weekly and 0.8 mg/kg once weekly in JIA patients are of the same magnitude as the differences observed between twice weekly and weekly regimens in adult RA patients.

In clinical studies with etanercept, pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients. The pharmacokinetics of etanercept were unaltered by concomitant MTX in RA patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on etanercept disposition.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept products or their effect on fertility. Mutagenesis studies were conducted with etanercept *in vitro* and *in vivo*, and no evidence of mutagenic activity was observed.

14 CLINICAL STUDIES

14.1 Adult Rheumatoid Arthritis

The safety and efficacy of etanercept were assessed in four randomized, double-blind, controlled studies. The results of all four trials were expressed in percentage of patients with improvement in RA using ACR response criteria.

Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs) (e.g., hydroxychloroquine, oral or injectable gold, MTX, azathioprine, D-penicillamine, sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr, C-reactive protein (CRP) > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg etanercept or placebo were administered SC twice a week for 6 consecutive months.

Study II evaluated 89 patients and had similar inclusion criteria to Study I except that patients in Study II had additionally received MTX for at least 6 months with a stable dose (12.5 to 25 mg/week) for at least 4 weeks and they had at least 6 tender or painful joints. Patients in Study II received a dose of 25 mg etanercept or placebo SC twice a week for 6 months in addition to their stable MTX dose.

Study III compared the efficacy of etanercept to MTX in patients with active RA. This study evaluated 632 patients who were ≥ 18 years old with early (≤ 3 years disease duration) active RA, had never received treatment with MTX, and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg etanercept were administered SC twice a week for 12 consecutive months. The study was unblinded after all patients had completed at least 12 months (and a median of 17.3 months) of therapy. The majority of patients remained in the study on the treatment to which they were randomized through 2 years, after which they entered an extension study and received open-label 25 mg etanercept. MTX tablets (escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial) or placebo tablets were given once a week on the same day as the injection of placebo or etanercept doses, respectively.

Study IV evaluated 682 adult patients with active RA of 6 months to 20 years duration (mean of 7 years) who had an inadequate response to at least one DMARD other than MTX. Forty-three percent of patients had previously received MTX for a mean of 2 years prior to the trial at a mean dose of 12.9 mg. Patients were excluded from this study if MTX had been discontinued for lack of efficacy or for safety considerations. The patient baseline characteristics were similar to those of patients in Study I. Patients were randomized to MTX alone (7.5 to 20 mg weekly, dose escalated as described for Study III; median dose 20 mg), etanercept alone (25 mg twice

weekly), or the combination of etanercept and MTX initiated concurrently (at the same doses as above). The study evaluated ACR response, Sharp radiographic score, and safety.

Clinical Response

A higher percentage of patients treated with etanercept and etanercept in combination with MTX achieved ACR 20, ACR 50, and ACR 70 responses and Major Clinical Responses than in the comparison groups. The results of Studies I, II, and III are summarized in Table 6. The results of Study IV are summarized in Table 7.

Table 6. ACR Responses in Placebo- and Active-Controlled Trials (Percent of Patients)

Response	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
	Placebo N=80	Etanercept[a] N= 78	MTX/Placebo N= 30	MTX/Etanercept[a] N= 59	MTX N= 217	Etanercept[a] N= 207
ACR 20						
Month 3	23%	62%	33%	66%	56%	62%
Month 6	11%	59%	27%	71%	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
ACR 50						
Month 3	8%	41%	0%	42%	24%	29%
Month 6	5%	40%	3%	39%	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
ACR 70						
Month 3	4%	15%	0%	15%	7%	13%
Month 6	1%	15%	0%	15%	14%	21%
Month 12	NA	NA	NA	NA	22%	25%

[a] 25 mg etanercept SC twice weekly
[b] $p < 0.01$, etanercept vs placebo
[c] $p < 0.05$, etanercept vs MTX

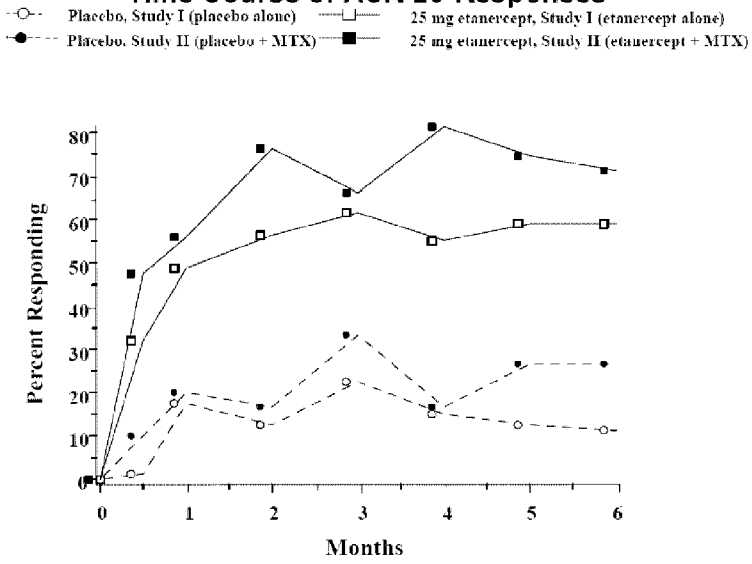
Table 7. Study IV Clinical Efficacy Results: Comparison of MTX vs Etanercept vs Etanercept in Combination With MTX in Patients With Rheumatoid Arthritis of 6 Months to 20 Years Duration (Percent of Patients)

Endpoint	MTX (N= 228)	Etanercept (N= 223)	Etanercept/MTX (N= 231)
ACR N[a,b]			
Month 12	40%	47%	63%[c]
ACR 20			
Month 12	59%	66%	75%[c]
ACR 50			
Month 12	36%	43%	63%[c]
ACR 70			
Month 12	17%	22%	40%[c]
Major Clinical Response[d]	6%	10%	24%[c]

[a]Values are medians.
[b]ACR N is the percent improvement based on the same core variables used in defining ACR 20, ACR 50, and ACR 70.
[c]$p < 0.05$ for comparisons of etanercept/MTX vs etanercept alone or MTX alone.
[d]Major clinical response is achieving an ACR 70 response for a continuous 6-month period.

The time course for ACR 20 response rates for patients receiving placebo or 25 mg etanercept in Studies I and II is summarized in Figure 1. The time course of responses to etanercept in Study III was similar.

Figure 1:
Time Course of ACR 20 Responses



Among patients receiving etanercept, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen in Studies I and III: 25 mg etanercept was more effective than 10 mg (10 mg was not evaluated in Study II). Etanercept was significantly better than placebo in all components of the ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness.

In Study III, ACR response rates and improvement in all the individual ACR response criteria were maintained through 24 months of etanercept therapy. Over the 2-year study, 23% of etanercept's patients achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period.

The results of the components of the ACR response criteria for Study I are shown in Table 8. Similar results were observed for etanercept -treated patients in Studies II and III.

Table 8. Components of ACR Response in Study I

	Placebo N= 80		**Etanercept[a] N= 78**	
Parameter (median)	**Baseline**	**3 Months**	**Baseline**	**3 Months[*]**
Number of tender joints[b]	34.0	29.5	31.2	10.0[f]
Number of swollen joints[c]	24.0	22.0	23.5	12.6[f]
Physician global assessment[d]	7.0	6.5	7.0	3.0[f]
Patient global assessment[d]	7.0	7.0	7.0	3.0[f]
Pain[d]	6.9	6.6	6.9	2.4[f]
Disability index[e]	1.7	1.8	1.6	1.0[f]
ESR (mm/hr)	31.0	32.0	28.0	15.5[f]
CRP (mg/dL)	2.8	3.9	3.5	0.9[f]

[*]Results at 6 months showed similar improvement.

[a]25 mg etanercept SC twice weekly.

[b]Scale 0-71.

[c]Scale 0-68.

[d]Visual analog scale: 0 = best; 10 = worst.

[e]Health Assessment Questionnaire: 0 = best; 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[f]$p < 0.01$, etanercept vs placebo, based on mean percent change from baseline.

After discontinuation of etanercept, symptoms of arthritis generally returned within a month. Reintroduction of treatment with etanercept after discontinuations of up to 18 months resulted in the same magnitudes of response as in patients who received etanercept without interruption of therapy, based on results of open-label studies.

Continued durable responses were seen for over 60 months in open-label extension treatment trials when patients received etanercept without interruption. A substantial number of patients who initially received concomitant MTX or corticosteroids were able to reduce their doses or discontinue these concomitant therapies while maintaining their clinical responses.

Physical Function Response

In Studies I, II, and III, physical function and disability were assessed using the Health Assessment Questionnaire (HAQ). Additionally, in Study III, patients were administered the SF-36 Health Survey. In Studies I and II, patients treated with 25 mg etanercept twice weekly showed greater improvement from baseline in the HAQ score beginning in month 1 through month 6 in comparison to placebo ($p < 0.001$) for the HAQ disability domain (where 0 = none and 3 = severe). In Study I, the mean improvement in the HAQ score from baseline to month 6 was 0.6 (from 1.6 to 1.0) for the 25 mg etanercept group and 0 (from 1.7 to 1.7) for the placebo group. In Study II, the mean improvement from baseline to month 6 was 0.6 (from 1.5 to 0.9) for the etanercept /MTX group and 0.2 (from 1.3 to 1.2) for the placebo/MTX group. In Study III, the mean improvement in the HAQ score from baseline to month 6 was 0.7 (from 1.5 to 0.7) for 25 mg etanercept twice weekly. All subdomains of the HAQ in Studies I and III were improved in patients treated with etanercept.

In Study III, patients treated with 25 mg etanercept twice weekly showed greater improvement from baseline in SF-36 physical component summary score compared to etanercept 10 mg twice weekly and no worsening in the SF-36 mental component summary score. In open-label studies of etanercept, improvements in physical function and disability measures have been maintained for up to 4 years.

In Study IV, median HAQ scores improved from baseline levels of 1.8, 1.8, and 1.8 to 1.1, 1.0, and 0.6 at 12 months in the MTX, etanercept, and etanercept /MTX combination treatment groups, respectively (combination versus both MTX and etanercept, $p < 0.01$). Twenty-nine percent of patients in the MTX alone treatment group had an improvement of HAQ of at least 1 unit versus 40% and 51% in etanercept alone and etanercept /MTX combination treatment groups, respectively.

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing (JSN) score. Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months, 12 months, and 24 months and scored by readers who were unaware of treatment group. The results are shown in Table 9. A significant difference for change in erosion score was observed at 6 months and maintained at 12 months.

Table 9. Mean Radiographic Change Over 6 and 12 Months in Study III

		MTX	25 mg Etanercept	MTX/Etanercept (95% Confidence Interval*)	P Value
12 Months	Total Sharp Score	1.59	1.00	0.59 (-0.12, 1.30)	0.1
	Erosion Score	1.03	0.47	0.56 (0.11, 1.00)	0.002
	JSN Score	0.56	0.52	0.04 (-0.39, 0.46)	0.5
6 Months	Total Sharp Score	1.06	0.57	0.49 (0.06, 0.91)	0.001
	Erosion Score	0.68	0.30	0.38 (0.09, 0.66)	0.001
	JSN Score	0.38	0.27	0.11 (-0.14, 0.35)	0.6

* 95% confidence intervals for the differences in change scores between MTX and etanercept.

Patients continued on the therapy to which they were randomized for the second year of Study III. Seventy-two percent of patients had x-rays obtained at 24 months. Compared to the patients in the MTX group, greater inhibition of progression in TSS and erosion score was seen in the 25 mg etanercept group, and, in addition, less progression was noted in the JSN score.

In the open-label extension of Study III, 48% of the original patients treated with 25 mg etanercept have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage, as measured by the TSS, and 55% of them had no progression of structural damage. Patients originally treated with MTX had further reduction in radiographic progression once they began treatment with etanercept.

In Study IV, less radiographic progression (TSS) was observed with etanercept in combination with MTX compared with etanercept alone or MTX alone at month 12 (Table 10). In the MTX treatment group, 55% of patients experienced no radiographic progression (TSS change $\leq$ 0.0) at 12 months compared to 63% and 76% in etanercept alone and etanercept /MTX combination treatment groups, respectively.

Table 10. Mean Radiographic Change in Study IV at 12 Months (95% Confidence Interval)

	MTX (N= 212)	Etanercept (N=212)*	Etanercept/MTX (N=218)*
Total Sharp Score (TSS)	2.80	0.52[a]	-0.54[b,c]

	(1.08, 4.51)	(-0.10, 1.15)	(-1.00, -0.07)
Erosion Score (ES)	1.68	0.21[a]	-0.30[b]
	(0.61, 2.74)	(-0.20, 0.61)	(-0.65, 0.04)
Joint Space Narrowing (JSN) Score	1.12	0.32	-0.23[b,c]
	(0.34, 1.90)	(0.00, 0.63)	(-0.45, -0.02)

[*] Analyzed radiographic ITT population.
[a] $p < 0.05$ for comparison of etanercept vs MTX.
[b] $p < 0.05$ for comparison of etanercept/MTX vs MTX.
[c] $p < 0.05$ for comparison of etanercept/MTX vs etanercept.

Once Weekly Dosing

The safety and efficacy of 50 mg etanercept (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. Fifty-three patients received placebo, 214 patients received 50 mg etanercept once weekly, and 153 patients received 25 mg etanercept twice weekly. The safety and efficacy profiles of the two etanercept treatment groups were similar.

14.2 Polyarticular Juvenile Idiopathic Arthritis (JIA)

The safety and efficacy of etanercept were assessed in a 2-part study in 69 children with polyarticular JIA who had a variety of JIA onset types. Patients ages 2 to 17 years with moderately to severely active polyarticular JIA refractory to or intolerant of MTX were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) etanercept SC twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on etanercept or receive placebo for 4 months and assessed for disease flare. Responses were measured using the JIA Definition of Improvement (DOI), defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of the six JIA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and ESR. Disease flare was defined as a ≥ 30% worsening in three of the six JIA core set criteria and ≥ 30% improvement in not more than one of the six JIA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on etanercept experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo ($p = 0.007$). From the start of part 2, the median time to flare was ≥ 116 days for patients who received etanercept and 28 days for patients who received placebo. Each component of the JIA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on etanercept. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some

of the patients remaining on etanercept continued to improve from month 3 through month 7, while those who received placebo did not improve.

The majority of JIA patients who developed a disease flare in part 2 and reintroduced etanercept treatment up to 4 months after discontinuation re-responded to etanercept therapy in open-label studies. Most of the responding patients who continued etanercept therapy without interruption have maintained responses for up to 48 months.

Studies have not been done in patients with polyarticular JIA to assess the effects of continued etanercept therapy in patients who do not respond within 3 months of initiating etanercept therapy, or to assess the combination of etanercept with MTX.

14.3 Psoriatic Arthritis

The safety and efficacy of etanercept were assessed in a randomized, double-blind, placebo-controlled study in 205 patients with PsA. Patients were between 18 and 70 years of age and had active PsA (≥ 3 swollen joints and ≥ 3 tender joints) in one or more of the following forms: (1) distal interphalangeal (DIP) involvement (N = 104); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis; N = 173); (3) arthritis mutilans (N = 3); (4) asymmetric psoriatic arthritis (N = 81); or (5) ankylosing spondylitis-like (N = 7). Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients on MTX therapy at enrollment (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week MTX. Doses of 25 mg etanercept or placebo were administered SC twice a week during the initial 6-month double-blind period of the study. Patients continued to receive blinded therapy in an up to 6-month maintenance period until all patients had completed the controlled period. Following this, patients received open-label 25 mg etanercept twice a week in a 12-month extension period.

Compared to placebo, treatment with etanercept resulted in significant improvements in measures of disease activity (Table 11).

Table 11. Components of Disease Activity in Psoriatic Arthritis

	Placebo N= 104		Etanercept[a] N= 101	
Parameter (median)	Baseline	6 Months	Baseline	6 Months
Number of tender joints[b]	17.0	13.0	18.0	5.0
Number of swollen joints[c]	12.5	9.5	13.0	5.0
Physician global assessment[d]	3.0	3.0	3.0	1.0
Patient global assessment[d]	3.0	3.0	3.0	1.0
Morning stiffness (minutes)	60	60	60	15
Pain[d]	3.0	3.0	3.0	1.0
Disability index[e]	1.0	0.9	1.1	0.3
CRP (mg/dL)[f]	1.1	1.1	1.6	0.2

[a] $p < 0.001$ for all comparisons between etanercept and placebo at 6 months.
[b] Scale 0-78.
[c] Scale 0-76.
[d] Likert scale: 0 = best; 5 = worst.
[e] Health Assessment Questionnaire: 0 = best; 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[f] Normal range: 0-0.79 mg/dL.

Among patients with PsA who received etanercept, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline. At 6 months, the ACR 20/50/70 responses were achieved by 50%, 37%, and 9%, respectively, of patients receiving etanercept, compared to 13%, 4%, and 1%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of PsA, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. The results of this study were similar to those seen in an earlier single-center, randomized, placebo-controlled study of 60 patients with PsA.

The skin lesions of psoriasis were also improved with etanercept, relative to placebo, as measured by percentages of patients achieving improvements in the Psoriasis Area and Severity Index (PASI). Responses increased over time, and at 6 months, the proportions of patients achieving a 50% or 75% improvement in the PASI were 47% and 23%, respectively, in the etanercept group (N = 66), compared to 18% and 3%, respectively, in the placebo group (N = 62). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Radiographic Response

Radiographic changes were also assessed in the PsA study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. A modified Total Sharp Score (TSS), which included distal interphalangeal joints (ie, not identical to the modified TSS used for RA) was used by readers blinded to treatment group to assess the radiographs. Some radiographic features specific to PsA (eg, pencil-and-cup deformity, joint space widening, gross osteolysis, and ankylosis) were included in the scoring system, but others (eg, phalangeal tuft resorption, juxta-articular and shaft periostitis) were not.

Most patients showed little or no change in the modified TSS during this 24-month study (median change of 0 in both patients who initially received etanercept or placebo). More placebo-treated patients experienced larger magnitudes of radiographic worsening (increased TSS) compared to etanercept treatment during the controlled period of the study. At 12 months, in an exploratory analysis, 12% (12 of 104) of placebo patients compared to none of the 101 of etanercept-treated patients had increases of 3 points or more in TSS. Inhibition of radiographic progression was maintained in patients who continued on etanercept during the second year. Of the patients with 1-year and 2-year x-rays, 3% (2 of 71) had increases of 3 points or more in TSS at 1 and 2 years.

Physical Function Response

In the PsA study, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 25 mg etanercept twice weekly showed greater improvement from baseline in the HAQ-DI score (mean decreases of 54% at both months 3 and 6) in comparison to placebo (mean decreases of 6% at both months 3 and 6) ($p < 0.001$). At months 3 and 6, patients treated with etanercept showed greater improvement from baseline in the SF-36 physical component summary score compared to patients treated with placebo, and no worsening in the SF-36 mental component summary score. Improvements in physical function and disability measures were maintained for up to 2 years through the open-label portion of the study.

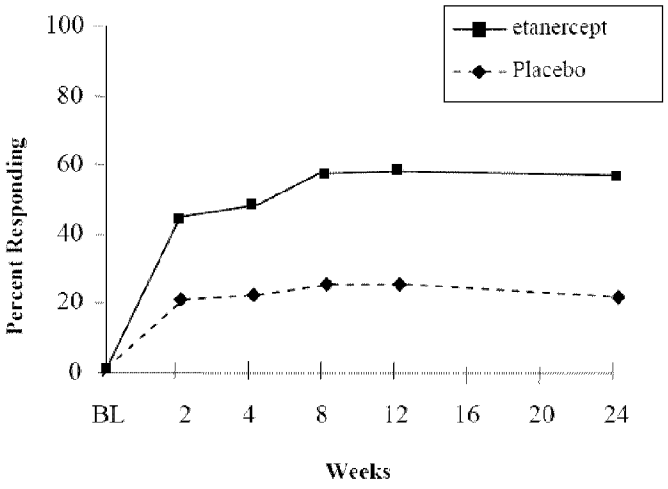
14.4 Ankylosing Spondylitis

The safety and efficacy of etanercept were assessed in a randomized, double-blind, placebo-controlled study in 277 patients with active AS. Patients were between 18 and 70 years of age and had AS as defined by the modified New York Criteria for Ankylosing Spondylitis. Patients were to have evidence of active disease based on values of $\geq$ 30 on a 0-100 unit Visual Analog Scale (VAS) for the average of morning stiffness duration and intensity, and two of the following three other parameters: a) patient global assessment, b) average of nocturnal and total back pain, and c) the average score on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients with complete ankylosis of the spine were excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate, or prednisone ($\leq$ 10 mg/day) could continue

these drugs at stable doses for the duration of the study. Doses of 25 mg etanercept or placebo were administered SC twice a week for 6 months.

The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS) response criteria. Compared to placebo, treatment with etanercept resulted in improvements in the ASAS and other measures of disease activity (Figure 2 and Table 12).

Figure 2. ASAS 20 Responses in Ankylosing Spondylitis



At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 45%, and 29%, respectively, of patients receiving etanercept, compared to 27%, 13%, and 7%, respectively, of patients receiving placebo ($p \leq 0.0001$, etanercept vs placebo). Similar responses were seen at week 24. Responses were similar between those patients receiving concomitant therapies at baseline and those who were not. The results of this study were similar to those seen in a single-center, randomized, placebo-controlled study of 40 patients and a multicenter, randomized, placebo-controlled study of 84 patients with AS.

Table 12. Components of Ankylosing Spondylitis Disease Activity

	Placebo N= 139		Etanercept[a] N= 138	
Median values at time points	Baseline	6 Months	Baseline	6 Months
ASAS response criteria				
Patient global assessment[b]	63	56	63	36
Back pain[c]	62	56	60	34
BASFI[d]	56	55	52	36
Inflammation[e]	64	57	61	33
Acute phase reactants				
CRP (mg/dL)[f]	2.0	1.9	1.9	0.6
Spinal mobility (cm):				
Modified Schober's test	3.0	2.9	3.1	3.3
Chest expansion	3.2	3.0	3.3	3.9
Occiput-to-wall measurement	5.3	6.0	5.6	4.5

[a] $p < 0.0015$ for all comparisons between etanercept and placebo at 6 months. P values for continuous endpoints were based on percent change from baseline.
[b] Measured on a Visual Analog Scale (VAS) with 0 = "none" and 100 = "severe".
[c] Average of total nocturnal and back pain scores, measured on a VAS with 0 = "no pain" and 100 = "most severe pain".
[d] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions.
[e] Inflammation represented by the average of the last 2 questions on the 6-question Bath Anklyosing Spondylitis Disease Activity Index (BASDAI).
[f] C-reactive protein (CRP) normal range: 0-1.0 mg/dL.

14.5 Plaque Psoriasis

The safety and efficacy of etanercept were assessed in two randomized, double-blind, placebo-controlled studies in adults with chronic stable PsO involving ≥ 10% of the body surface area, a minimum Psoriasis Area and Severity Index (PASI) score of 10 and who had received or were candidates for systemic antipsoriatic therapy or phototherapy. Patients with guttate, erythrodermic, or pustular psoriasis and patients with severe infections within 4 weeks of screening were excluded from study. No concomitant major antipsoriatic therapies were allowed during the study.

Study I evaluated 672 patients who received placebo or etanercept SC at doses of 25 mg once a week, 25 mg twice a week, or 50 mg twice a week for 3 months. After 3 months, patients continued on blinded treatments for an additional 3 months during which time patients originally randomized to placebo began treatment with blinded etanercept at 25 mg twice weekly (designated as placebo/etanercept in Table 13); patients originally randomized to etanercept continued on the originally randomized dose (designated as etanercept/etanercept groups in Table 13).

Study II evaluated 611 patients who received placebo or etanercept SC at doses of 25 mg or 50 mg twice a week for 3 months. After 3 months of randomized, blinded treatment, patients in all three arms began receiving open-label etanercept at 25 mg twice weekly for 9 additional months.

Response to treatment in both studies was assessed after 3 months of therapy and was defined as the proportion of patients who achieved a reduction in PASI score of at least 75% from baseline. The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling).

Other evaluated outcomes included the proportion of patients who achieved a score of "clear" or "minimal" by the Static Physician Global Assessment (sPGA) and the proportion of patients with a reduction of PASI of at least 50% from baseline. The sPGA is a 6-category scale ranging from "5 = severe" to "0 = none" indicating the physician's overall assessment of the PsO severity focusing on induration, erythema and scaling. Treatment success of "clear" or "minimal" consisted of none or minimal elevation in plaque, up to faint red coloration in erythema and none or minimal fine scale over < 5% of the plaque.

Patients in all treatment groups and in both studies had a median baseline PASI score ranging from 15 to 17, and the percentage of patients with baseline sPGA classifications ranged from 54% to 66% for moderate, 17% to 26% for marked and 1% to 5% for severe. Across all treatment groups, the percentage of patients who previously received systemic therapy for PsO ranged from 61% to 65% in Study I and 71% to 75% in Study II, and those who previously received phototherapy ranged from 44% to 50% in Study I and 72% to 73% in Study II.

More patients randomized to etanercept than placebo achieved at least a 75% reduction from baseline PASI score (PASI 75) with a dose response relationship across doses of 25 mg once a week, 25 mg twice a week and 50 mg twice a week (Tables 13 and 14). The individual components of the PASI (induration, erythema and scaling) contributed comparably to the overall treatment-associated improvement in PASI.

Table 13. Study I Outcomes at 3 and 6 months

		Etanercept/Etanercept		
	Placebo/Etanercept 25 mg BIW (N= 168)	**25 mg QW (N= 169)**	**25 mg BIW (N= 167)**	**50 mg BIW (N= 168)**
3 Months				
PASI 75 n (%)	6 (4%)	23 (14%)[a]	53 (32%)[b]	79 (47%)[b]
Difference (95% CI)		10% (4, 16)	28% (21, 36)	43% (35, 52)
sPGA, 'clear' or 'minimal' n (%)	8 (5%)	36 (21%)[b]	53 (32%)[b]	79 (47%)[b]
Difference (95% CI)		17% (10, 24)	27% (19, 35)	42% (34, 50)
PASI 50 n (%)	24 (14%)	62 (37%)[b]	90 (54%)[b]	119 (71%)[b]
Difference (95% CI)		22% (13, 31)	40% (30, 49)	57% (48, 65)
6 Months				
PASI 75 n (%)	55 (33%)	36 (21%)	68 (41%)	90 (54%)

[a] $p = 0.001$ compared with placebo.
[b] $p < 0.0001$ compared with placebo.

Table 14. Study II Outcomes at 3 Months

		Etanercept	
	Placebo (N= 204)	**25 mg BIW (N= 204)**	**50 mg BIW (N= 203)**
PASI 75 n (%)	6 (3%)	66 (32%)[a]	94 (46%)[a]
Difference (95% CI)		29% (23, 36)	43% (36, 51)
sPGA, "clear" or minimal" n (%)	7 (3%)	75 (37%)[a]	109 (54%)[a]
Difference (95% CI)		34% (26, 41)	50% (43, 58)
PASI 50 n (%)	18 (9%)	124 (61%)[a]	147 (72%)[a]
Difference (95% CI)		52% (44, 60)	64% (56, 71)

[a] $p < 0.0001$ compared with placebo.

Among PASI 75 achievers in both studies, the median time to PASI 50 and PASI 75 was approximately 1 month and approximately 2 months, respectively, after the start of therapy with either 25 or 50 mg twice a week.

In Study I, patients who achieved PASI 75 at month 6 were entered into a study drug withdrawal and retreatment period. Following withdrawal of study drug, these patients had a median duration of PASI 75 of between 1 and 2 months.

In Study I, among patients who were PASI 75 responders at 3 months, retreatment with their original blinded etanercept dose after discontinuation of up to 5 months resulted in a similar proportion of responders as in the initial double-blind portion of the study.

In Study II, most patients initially randomized to 50 mg twice a week continued in the study after month 3 and had their etanercept dose decreased to 25 mg twice a week. Of the 91 patients who were PASI 75 responders at month 3, 70 (77%) maintained their PASI 75 response at month 6.

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program.

SEER Incidence Crude Rates, 13 Registries, 1992-2002.

16 HOW SUPPLIED/STORAGE AND HANDLING

Administration of one 50 mg ERELZI prefilled syringe with BD UltraSafe Passive Needle Guard or one ERELZI Sensoready Pen provides a dose equivalent to two 25 mg ERELZI prefilled syringes with BD UltraSafe Passive Needle Guard.

16.1 ERELZI Single-dose Prefilled Syringe with BD UltraSafe Passive Needle Guard and ERELZI Single-dose Prefilled Sensoready Pen

Each ERELZI (etanercept-szzs) Injection single-dose prefilled syringe with BD UltraSafe Passive Needle Guard and ERELZI single-dose prefilled Sensoready Pen contains clear and colorless to slightly yellow solution containing 25 mg/0.5 mL or 50 mg/mL of etanercept-szzs in a single-dose syringe with a 27-gauge, ½-inch needle.

50 mg/mL single-dose prefilled syringe	Carton of 1	NDC 61314-821-01
50 mg/mL single-dose prefilled syringe	Carton of 4	NDC 61314-821-04
50 mg/mL single-dose prefilled Sensoready Pen	Carton of 1	NDC 61314-832-01
50 mg/mL single-dose prefilled Sensoready Pen	Carton of 4	NDC 61314-832-04
25 mg/0.5 mL single-dose prefilled syringe	Carton of 1	NDC 61314-843-01
25 mg/0.5 mL single-dose prefilled syringe	Carton of 4	NDC 61314-843-04

ERELZI should be refrigerated at 36°F to 46°F (2°C to 8°C). Do not use ERELZI beyond the expiration date stamped on the carton or barrel label. DO NOT SHAKE. Store ERELZI in the original carton to protect from light or physical damage.

For convenience, storage of individual syringes or Sensoready Pens at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum single period of 28 days is permissible, with protection from light and sources of heat. Once a syringe or Sensoready Pen has been stored at room temperature, it should not be placed back into the refrigerator. If not used within 28 days at room temperature, the syringe or Sensoready Pens should be discarded. Do not store ERELZI in extreme heat or cold. DO NOT FREEZE. Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling *[Medication Guide and Instructions for Use]*.

See Medication Guide

Patients or their caregivers should be provided the ERELZI "Medication Guide" and provided an opportunity to read it and ask questions prior to initiation of therapy. The healthcare provider

should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

17.1 Patient Counseling

Patients should be advised of the potential benefits and risks of ERELZI. Physicians should instruct their patients to read the Medication Guide before starting ERELZI therapy and to reread each time the prescription is renewed.

Infections

Inform patients that ERELZI may lower the ability of their immune system to fight infections. Advise patients of the importance of contacting their doctor if they develop any symptoms of infection, tuberculosis or reactivation of hepatitis B virus infections.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions, such as central nervous system demyelinating disorders, heart failure or autoimmune disorders, such as lupus-like syndrome or autoimmune hepatitis. Counsel about the risk of lymphoma and other malignancies while receiving ERELZI. Advise patients to report any symptoms suggestive of a pancytopenia, such as bruising, bleeding, persistent fever or pallor.

Allergic Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the following components contain dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex: the needle cap of the prefilled syringe and the internal needle cover within the cap of the Sensoready Pen.

17.2 Administration of ERELZI

If a patient or caregiver is to administer ERELZI, the patient or caregiver should be instructed in injection techniques and how to measure and administer the correct dose [see the ERELZI (etanercept-szzs) "Instructions for Use" insert]. The first injection should be performed under the supervision of a qualified healthcare professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique, as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes.

A puncture-resistant container for disposal of needles, syringes and Sensoready Pens should be used.

Manufactured by:

Sandoz Inc.

Princeton, NJ 08540

US License No. 2003

At:
Novartis Pharma AG
Stein, Switzerland
Product of Austria

Medication Guide
ERELZI (eh rel' zee)
(etanercept-szzs)
injection, for Subcutaneous Use

Read the Medication Guide that comes with ERELZI before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. It is important to remain under your doctor's care while using ERELZI.

ERELZI is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker that affects your immune system.

What is the most important information I should know about ERELZI?

ERELZI may cause serious side effects, including:

1. Risk of Infection
2. Risk of Cancer

1. Risk of Infection

ERELZI can lower the ability of your immune system to fight infections. Some people have serious infections while taking etanercept products. These infections include tuberculosis (TB), and infections caused by viruses, fungi, or bacteria that spread throughout their body. Some people have died from these infections.

- Your doctor should test you for TB before starting ERELZI.
- Your doctor should monitor you closely for symptoms of TB during treatment with ERELZI even if you tested negative for TB.
- Your doctor should check you for symptoms of any type of infection before, during, and after your treatment with ERELZI.

You should not start taking ERELZI if you have any kind of infection unless your doctor says it is okay.

2. Risk of Cancer

- There have been cases of unusual cancers in children and teenage patients who started using TNF-blocking agents at less than 18 years of age.
- For children, teenagers, and adults taking TNF-blocker medicines, including ERELZI, the chances of getting lymphoma or other cancers may increase.
- People with rheumatoid arthritis or psoriasis, especially those with very active disease, may be more likely to get lymphoma.

Before starting ERELZI, be sure to talk to your doctor:

ERELZI may not be right for you. Before starting ERELZI, tell your doctor about all of your medical conditions, including:

Infections. Tell your doctor if you:

- have an infection. See **"What is the most important information I should know about ERELZI?"**
- are being treated for an infection.
- think you have an infection.
- have symptoms of an infection such as fever, sweats or chills, cough or flu-like symptoms, shortness of breath, blood in your phlegm, weight loss, muscle aches, warm, red or painful areas on your skin, sores on your body, diarrhea or stomach pain, burning when you urinate or urinating more often than normal, and feel very tired.
- have any open cuts on your body.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- were born in, lived in, or traveled to countries where there is a risk for getting TB. Ask your doctor if you are not sure.
- live, have lived in, or traveled to certain parts of the country (such as the Ohio and Mississippi River valleys, or the Southwest) where there is a greater risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may happen or become more severe if you use ERELZI. Ask your doctor if you do not know if you live or have lived in an area where these infections are common.
- have or have had hepatitis B.

Also, BEFORE starting ERELZI, tell your doctor:

- **About all the medicines you take including prescription and over-the-counter medicines, vitamins and herbal supplements including:**
  - **Orencia® (abatacept) or Kineret® (anakinra)**. You have a higher chance for serious infections when taking ERELZI with Orencia® or Kineret®.
  - **Cyclophosphamide (Cytoxan®)**. You may have a higher chance for getting certain cancers when taking ERELZI

with cyclophosphamide.
- **Anti-diabetic medicines**. If you have diabetes and are taking medication to control your diabetes, your doctor may decide you need less anti-diabetic medicine while taking ERELZI.

Keep a list of all your medications with you to show your doctor and pharmacist each time you get a new medicine. Ask your doctor if you are not sure if your medicine is one listed above.

Other important medical information you should tell your doctor BEFORE starting ERELZI, includes if you:

- have or had a nervous system problem such as multiple sclerosis or Guillain-Barré syndrome.
- have or had heart failure.
- are scheduled to have surgery.
- have recently received or are scheduled to receive a vaccine.
  - All vaccines should be brought up-to-date before starting ERELZI.
  - People taking ERELZI should not receive live vaccines.
  - Ask your doctor if you are not sure if you received a live vaccine.
- are allergic to rubber or latex.
  - The internal needle cover within the cap of the Sensoready® Pen and the needle cap of the prefilled syringe contains latex.
- have been around someone with varicella zoster (chicken pox).
- are pregnant or plan to become pregnant. It is not known if ERELZI will harm your unborn baby. If you took ERELZI during pregnancy, talk to your doctor prior to the administration of live vaccines to your infant.
- are breastfeeding or plan to breastfeed. ERELZI can pass into breast milk. You and your doctor should decide if you will take ERELZI or breastfeed. You should not do both.

See **"What are the possible side effects of ERELZI?" below for more information.**

What is ERELZI?

ERELZI is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker.

ERELZI is used to treat:

- moderately to severely active rheumatoid arthritis (RA). ERELZI can be used alone or with a medicine called methotrexate.
- psoriatic arthritis. ERELZI can be used alone or with methotrexate.
- ankylosing spondylitis (AS).
- chronic moderate to severe plaque psoriasis in adults ages 18 years and older.
- moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in children ages 2 years and older.

You may continue to use other medicines that help treat your condition while taking ERELZI, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as recommended by your doctor.

ERELZI can help reduce joint damage and the signs and symptoms of the above mentioned diseases. People with these diseases have too much of a protein called tumor necrosis factor (TNF), which is made by your immune system. ERELZI can reduce the effect of TNF in the body and block the damage that too much TNF can cause, but it can also lower the ability of your immune system to fight infections. See **"What is the most important information I should know about ERELZI?"** and **"What are the possible side effects of ERELZI?"**

Who should not use ERELZI?

Do not use ERELZI if you:

- have an infection that has spread through your body (sepsis).

How should I use ERELZI?

- ERELZI is given as an injection under the skin (subcutaneous or SC).
- If your doctor decides that you or a caregiver can give the injections of ERELZI at home, you or your caregiver should receive training on the right way to prepare and inject ERELZI. Do not try to inject ERELZI until you have been shown the right way by your doctor or nurse.
- ERELZI is available in the forms listed below. Your doctor will prescribe the type that is best for you.
  - Single-dose Prefilled Syringe
  - Single-dose Prefilled Sensoready® Pen
- See the Instructions for Use that come with ERELZI for detailed instructions about the right way to store, prepare, and give your ERELZI injections at home.
- Your doctor will tell you how often you should use ERELZI. Do not miss any doses of ERELZI. If you forget to use ERELZI, inject your dose as soon as you remember. Then, take your next dose at your regular(ly) scheduled time. In case you are not sure when to inject ERELZI, call your doctor or pharmacist. **Do not use ERELZI more often than as directed by your doctor.**

- Your child's dose of ERELZI depends on his or her weight. Your child's doctor will tell you which form of ERELZI to use and how much to give your child.

What are the possible side effects of ERELZI?
ERELZI can cause serious side effects including:

- See **"What is the most important information I should know about ERELZI?"**
- **Infections**. ERELZI can make you more likely to get infections or make any infection that you have worse. Call your doctor right away if you have any symptoms of an infection. See "**Before starting ERELZI, be sure to talk to your doctor**" for a list of symptoms of infection.
- **Previous Hepatitis B infection**. If you have been previously infected with the hepatitis B virus (a virus that affects the liver), the virus can become active while you use ERELZI. Your doctor may do a blood test before you start treatment with ERELZI and while you use ERELZI.
- **Nervous system problems**. Rarely, people who use TNF-blocker medicines have developed nervous system problems such as multiple sclerosis, seizures, or inflammation of the nerves of the eyes. Tell your doctor right away if you get any of these symptoms: numbness or tingling in any part of your body, vision changes, weakness in your arms and legs, and dizziness.
- **Blood problems**. Low blood counts have been seen with other TNF-blocker medicines. Your body may not make enough of the blood cells that help fight infections or help stop bleeding. Symptoms include fever, bruising or bleeding very easily, or looking pale.
- **Heart failure including new heart failure or worsening of heart failure you already have**. New or worse heart failure can happen in people who use TNF-blocker medicines like ERELZI. If you have heart failure your condition should be watched closely while you take ERELZI. Call your doctor right away if you get new or worsening symptoms of heart failure while taking ERELZI, such as shortness of breath or swelling of your lower legs or feet.
- **Psoriasis**. Some people using etanercept products developed new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps that may be filled with pus. Your doctor may decide to stop your treatment with ERELZI.
- **Allergic reactions**. Allergic reactions can happen to people who use TNF-blocker medicines. Call your doctor right away if you have any symptoms of an allergic reaction. Symptoms of an allergic reaction include a severe rash, a swollen face, or trouble breathing.
- **Autoimmune reactions, including**:
  - **Lupus-like syndrome**. Symptoms include a rash on your face and arms that gets worse in the sun. Tell your doctor if you have this symptom. Symptoms may go away when you stop using ERELZI.
  - **Autoimmune hepatitis**. Liver problems can happen in people who use TNF-blocker medicines, including ERELZI. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms: feel very tired, skin or eyes look yellow, poor appetite or vomiting, pain on the right side of your stomach (abdomen).

Common side effects of ERELZI include:

- **Injection site reactions** such as redness, swelling, itching, or pain. These symptoms usually go away within 3 to 5 days. If you have pain, redness, or swelling around the injection site that does not go away or gets worse, call your doctor.
- **Upper respiratory infections** (sinus infections).
- **Headache**.

These are not all the side effects with ERELZI. Tell your doctor about any side effect that bothers you or does not go away.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ERELZI?

- Store ERELZI in the refrigerator between 36°F to 46°F (2°C to 8°C).
- If needed, you may store the ERELZI syringe or pen, at room temperature between 68°F to 77°F (20°C to 25°C) for up to 28 days.
  - Once ERELZI has reached room temperature, do not put it back in the refrigerator.
- Throw away ERELZI that has been stored at room temperature after 28 days.
- **Do not** take ERELZI if the expiration date on the carton or barrel label of the prefilled syringe or pen has passed. Throw away ERELZI if the expiration date has passed.
- **Do not** store ERELZI in extreme heat or cold such as in your vehicle's glove box or trunk.
- **Do not freeze**.
- **Do not shake**.

- Store ERELZI in the original carton to protect from light or physical damage.
- Keep ERELZI and all medicines out of the reach of children.

General Information about the safe and effective use of ERELZI.

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use ERELZI for a condition for which it was not prescribed. Do not give ERELZI to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about ERELZI. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ERELZI that was written for healthcare professionals.

What are the ingredients in ERELZI?

Single-dose Prefilled Syringe and the Single-dose Prefilled Sensoready® Pen:

Active Ingredient: etanercept-szzs

Inactive Ingredients: sodium citrate, sucrose, sodium chloride, lysine, citric acid

Manufactured by: Sandoz Inc. Princeton, NJ 08540. US License No. 2003
At: Novartis Pharma AG. Stein, Switzerland. Product of Austria.
For more information, go to www.ERELZI.com or call 1-800-252-8747.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 08/2016

Instructions for Use

ERELZI (eh rel' zee)

(etanercept-szzs)

Sensoready® Pen

Be sure that you read, understand, and follow this Instructions for Use before injecting ERELZI. Your healthcare provider should show you how to prepare and inject ERELZI properly using the ERELZI Sensoready Pen before you use it for the first time. Talk to your healthcare provider if you have any questions.

Important:

- **Do not use** the ERELZI Sensoready Pen if either the seal on the outer carton or the seal on the pen is broken. Keep the ERELZI Sensoready Pen in the sealed outer carton until you are ready to use it.
- Inject ERELZI 15 to 30 minutes after taking it out of the refrigerator.
- **Do not shake** the ERELZI Sensoready Pen.
- **The internal needle cover within the cap of the ERELZI Sensoready Pen contains latex. Do not handle the ERELZI Sensoready Pen if you are sensitive to latex.**
- If you drop your ERELZI Sensoready Pen, **do not use** it if the ERELZI Sensoready Pen looks damaged, or if you dropped it with the cap removed.
- Throw away (dispose of) the used ERELZI Sensoready Pen right away after use. **Do not reuse a ERELZI Sensoready Pen.** See **"How should I dispose of used ERELZI Sensoready Pens?"** at the end of this Instructions for Use.

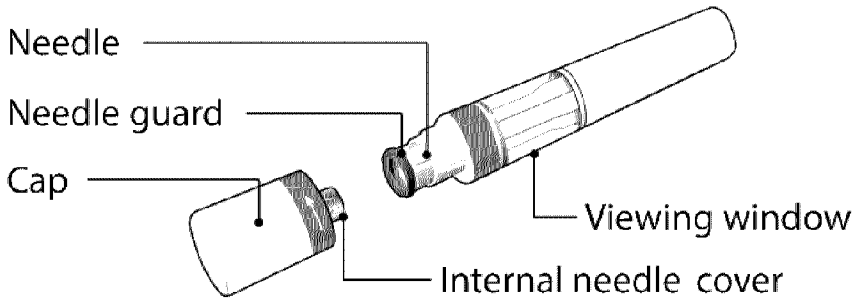
How should I store ERELZI?

- Store your carton of ERELZI Sensoready Pens in the refrigerator, between 36°F to 46°F (2°C to 8°C).
- If needed, you may store the ERELZI Sensoready Pen at room temperature between 68°F to 77°F (20°C to 25°C) for up to 28 days. Once the ERELZI Sensoready Pen has reached room temperature, do not put it back into the refrigerator. Throw away the ERELZI Sensoready Pen that has been stored at room temperature after 28 days.
- Keep ERELZI Sensoready Pen in the original carton until ready to use to protect from light.
- Do not store ERELZI in extreme heat or cold such as in your vehicle's glove box or trunk.
- Do not freeze ERELZI Sensoready Pen.

Keep ERELZI and all medicines out of the reach of children.

ERELZI Sensoready Pen parts (**see Figure A**):

Figure A



The ERELZI Sensoready Pen is shown above with the cap removed. **Do not** remove the cap until you are ready to inject.

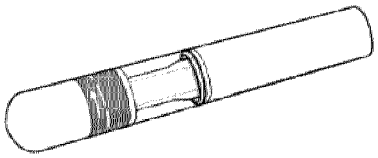
What you need for your injection:

Included in your carton:

A new ERELZI Sensoready Pen (**see Figure B**).

Each ERELZI Sensoready Pen contains 50 mg/mL of ERELZI.

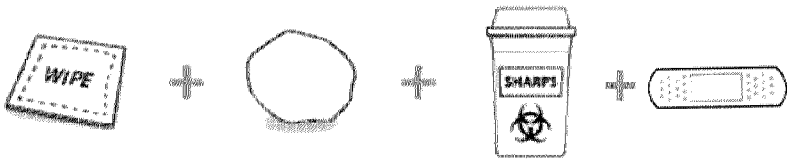
Figure B



Not included in your carton (**see Figure C**):

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container
- 1 Adhesive bandage

Figure C



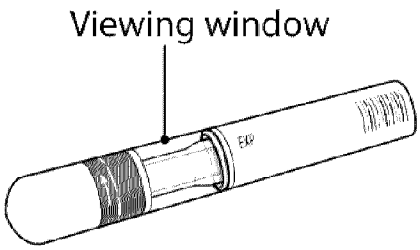
See "**How should I dispose of used ERELZI Sensoready Pen?**" at the end of this Instructions for Use.

Before your injection:

Take the ERELZI Sensoready Pen out of the refrigerator **15 to 30 minutes before injecting** to allow it to reach room temperature. **Do not** try to warm the ERELZI Sensoready Pen by using a heat source such as hot water or a microwave.

Step 1. Important safety checks before you inject (see Figure D):

Figure D



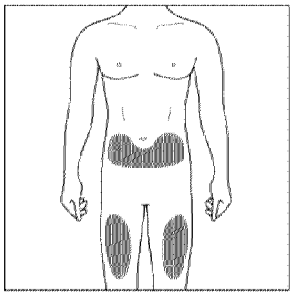
- Look through the viewing window. The liquid should be clear and colorless to slightly yellow. It is normal to see small white particles in the liquid. **Do not use** if the liquid is cloudy, discolored, or has large lumps, flakes, or particles in it. Return the ERELZI Sensoready Pen and the package it came in to your pharmacy. Contact your pharmacist if you are concerned about how the liquid in your ERELZI Sensoready Pen looks.
- Look at the **expiration date (EXP)** on your ERELZI Sensoready Pen. **Do not** use your ERELZI Sensoready Pen if the expiration date has passed. If the expiration date has passed, return the ERELZI Sensoready Pen and the package it came in to your pharmacy.

Contact your pharmacist if the ERELZI Sensoready Pen fails any of these checks.

Step 2. Choose your injection site:

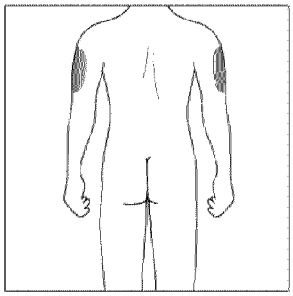
- The recommended site is the front of the thighs. You may also use the lower abdomen, but **not** the area 2 inches (5 cm) around your navel (belly button) **(see Figure E).**
- Choose a different site each time you give yourself an injection.
- Do not inject into areas where the skin is tender, bruised, red, scaly, or hard. Avoid areas with scars or stretch marks. If you have psoriasis, **do not** inject directly into any raised, thick, red, or scaly skin patches or lesions.

Figure E



- If a **caregiver or healthcare provider** is giving your injection, they may also inject into your upper arm **(see Figure F).**

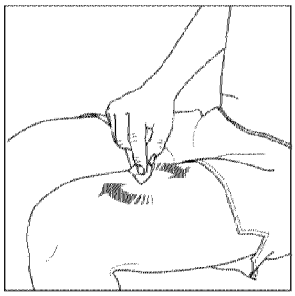
Figure F



Step 3. Cleaning your injection site:

- Wash your hands well with soap and water.
- Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting **(see Figure G)**.
- Do not touch the cleaned area again before injecting.

Figure G

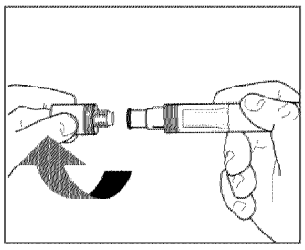


Your injection:

Step 4. Removing the cap:

- Only remove the cap when you are ready to use the ERELZI Sensoready Pen.
- Twist off the cap in the direction of the arrow **(see Figure H)**.
- Throw away the cap. **Do not try to reattach the cap.**
- Use the ERELZI Sensoready Pen within 5 minutes of removing the cap.

Figure H



Step 5. Holding your Sensoready Pen:

- Hold the ERELZI Sensoready Pen at a 90 degree angle to the clean injection site **(see Figure I)**.

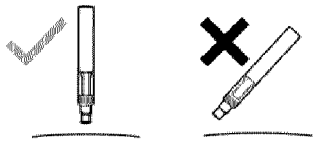
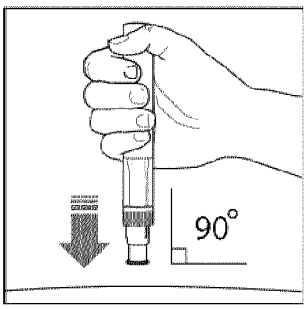


Figure I



Important: During the injection you will hear **2 loud clicks**:

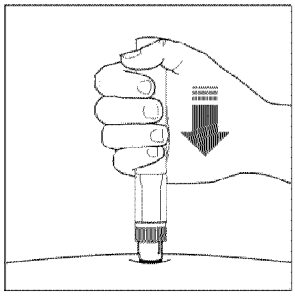
- The **1st click** indicates that **the injection has started**.
- Several seconds later a **2nd click** will indicate that **the injection is almost finished**.

You must keep holding the ERELZI Sensoready Pen firmly against your skin until you see a **green indicator** fill the viewing window and stop moving.

Step 6. Starting your injection:

- Press the ERELZI Sensoready Pen firmly against the skin to start the injection **(see Figure J)**.
- The **1st click** indicates the injection has started.
- **Keep holding** the ERELZI Sensoready Pen firmly against your skin.
- The **green indicator** shows the progress of the injection.

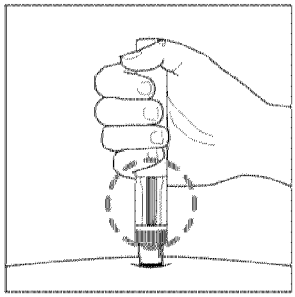
Figure J



Step 7. Completing your injection:

- Listen for the **2nd click**. This indicates the injection is **almost** finished.
- Check to make sure the **green indicator** fills the viewing window and has stopped moving **(see Figure K)**.
- The ERELZI Sensoready Pen can now be removed.

Figure K

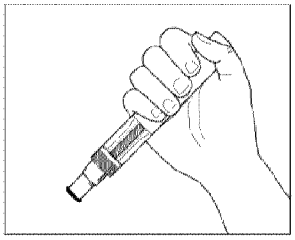


After your injection:

Step 8. Check the green indicator to make sure it fills the viewing window (see Figure L):

- This means the medicine has been delivered. Contact your healthcare provider if the green indicator is not visible.
- There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

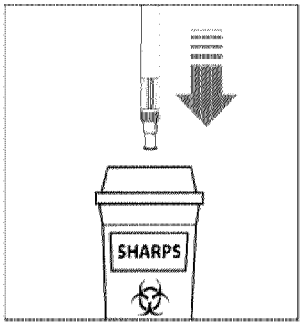
Figure L



How should I dispose of used ERELZI Sensoready Pens?

Step 9. Put your used ERELZI Sensoready Pens in an FDA-cleared sharps disposal container right away after use (**see Figure M**). **Do not throw away (dispose of)** ERELZI Sensoready Pens in your household trash.

Figure M



If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps container is almost full, you will need to follow your community guidelines, for the right way to dispose of your sharps disposal container. There may be a state or local laws about how you should throw away used syringes, needles and ERELZI Sensoready Pens. For more information about safe sharps disposal, and for specific information about sharps disposal, in the state that you live in, go to FDA's website at: http://www.fda.gov/safesharpsdisposal.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Sandoz Inc.
Princeton, NJ 08540
US License No. 2003

At:
Novartis Pharma AG
Stein, Switzerland
Product of Austria

Issued: August 2016

Instructions for Use

ERELZI (eh rel' zee)

(etanercept-szzs)

Prefilled Syringe

Important:

To help avoid a possible infection, you should follow these instructions.

Be sure that you read, understand, and follow this Instructions for Use before injecting ERELZI. Your healthcare provider should show you how to prepare and inject ERELZI properly using the prefilled syringe before you use it for the first time. Talk to your healthcare provider if you have any questions.

Important:

- **Do not use** the ERELZI prefilled syringe if the seal of the blister tray is broken.
- Keep the ERELZI prefilled syringe in the original carton to protect from light or damage until you are ready to use it.
- Inject ERELZI 15 to 30 minutes after taking it out of the refrigerator.
- **Do not shake** the ERELZI prefilled syringe.
- **The needle cap on the prefilled syringe contains latex. Do not handle the prefilled syringe if you are sensitive to latex.**
- The prefilled syringe has a needle guard that will be activated to cover the needle after the injection is given. The needle guard will help to prevent needle stick injuries to anyone who handles the prefilled syringe.
- Do not remove the needle cap until just before you give the injection.
- Avoid touching the needle guard wings before use. Touching them may cause the needle guard to be activated too early.
- Throw away (dispose of) the used ERELZI prefilled syringe right away after use. **Do not re-use a ERELZI prefilled syringe.** See **"How should I dispose of used ERELZI prefilled syringes?"** at the end of this Instructions for Use.

How should I store ERELZI?

- Store your carton of ERELZI prefilled syringes in the refrigerator, between 36°F to 46°F (2°C to 8°C).
- If needed, you may store the ERELZI prefilled syringe at room temperature between 68°F to 77°F (20°C to 25°C) for up to 28 days. Once the ERELZI prefilled syringe has reached room temperature, do not put it back into the refrigerator. Throw away the ERELZI prefilled syringe that has been stored at room temperature after 28 days.
- Keep ERELZI prefilled syringes in the original carton until ready to use to protect from light.
- Do not store ERELZI in extreme heat or cold such as in your vehicle's glove box or trunk.
- Do not freeze ERELZI prefilled syringes.

Keep ERELZI and all medicines out of the reach of children.

ERELZI prefilled syringe parts (see Figure A).

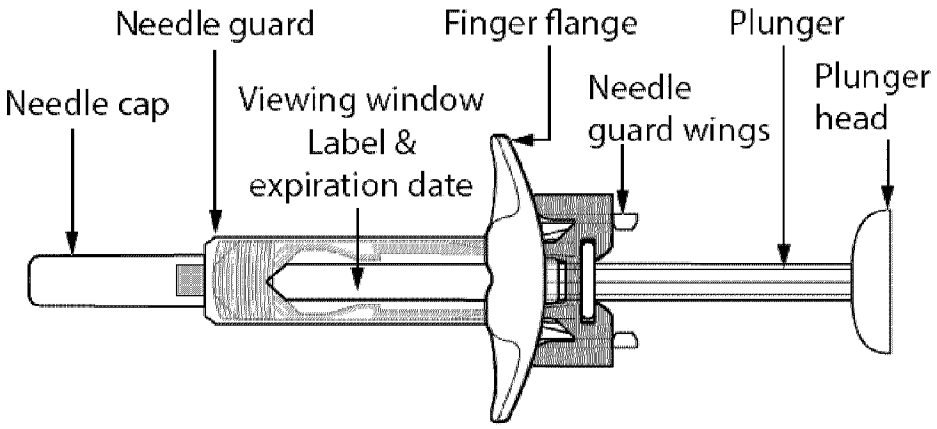


Figure A **ERELZI prefilled syringe with needle guard and finger flange**

- **In this configuration the Needle Guard is Activated- Do not use the pre-filled syringe (see Figure B)**

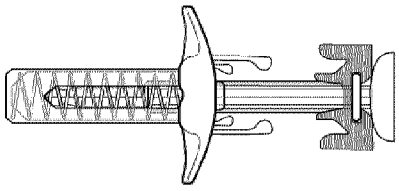


Figure B **Device Activated – Do Not Use**

- **In this configuration the Needle Guard is not activated and the prefilled syringe is ready for use (see Figure C)**

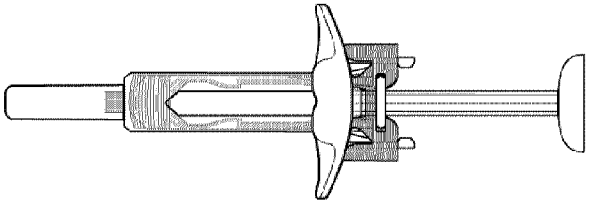


Figure C **Device Ready to Be Used**

What you need for your injection:

Included in the carton:

A new ERELZI prefilled syringe (**see Figure C**)

Each prefilled syringe contains 25 mg/0.5 mL or 50 mg/mL of ERELZI.

Not included in the carton (**see Figure D**):

Figure D

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container
- 1 Adhesive bandage

See **"How should I dispose of used ERELZI prefilled syringes?"** at the end of this Instructions for Use.

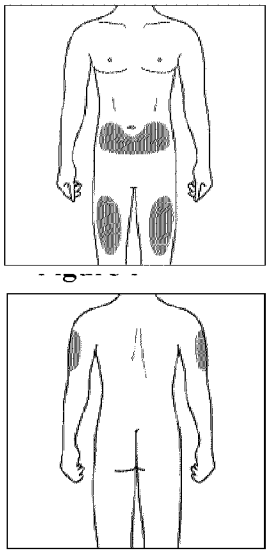
Step 1: Preparing the ERELZI Prefilled Syringe

1. Find a clean, well-lit, flat work surface, such as a table.
2. Take the blister containing the ERELZI prefilled syringe out of the refrigerator and leave it **unopened** on your work surface for about 15 to 30 minutes to allow it to reach room temperature. **Do not** try to warm the ERELZI prefilled syringe by using a heat source such as hot water or a microwave.
3. Wash your hands well with soap and water.
4. Take the ERELZI prefilled syringe out of the blister.
5. Look through the viewing window. The liquid should be clear and colorless to slightly yellow. It is normal to see small white particles in the liquid. **Do not use** if the liquid is cloudy, discolored, or has large lumps, flakes, or particles in it. Return the prefilled syringe and the package it came in to your pharmacy.
6. **Do not** use the ERELZI prefilled syringe if it is broken or the needle guard is activated. Return the prefilled syringe and the package it came in to your pharmacy.
7. **Do not** use the ERELZI prefilled syringe if the expiration date has passed. Return the prefilled syringe and the package it came in to your pharmacy.

Step 2: Choosing and Preparing an Injection Site

Figure E

1. The recommended site is the front of your thighs. You may also use the lower abdomen, but **not** the area 2 inches (5 cm) around your navel (belly button) (**see Figure E**).
2. Choose a different site each time you give yourself an injection.
3. **Do not** inject into areas where the skin is tender, bruised, red or hard. Avoid areas with scars or stretch marks.
4. If you have psoriasis, **do not** inject directly into any raised, thick, red, or scaly sk
5. If a **caregiver** or **healthcare provider** is giving you your injection, they may also inject into your outer upper arm (**see Figure F**).



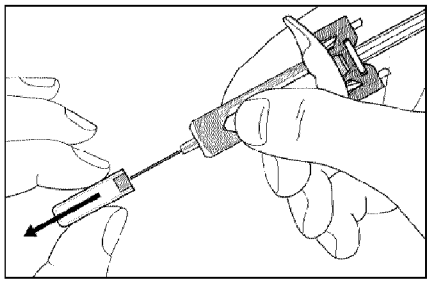
6. Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting. Do not touch the cleaned area again before injecting.

Step 3: Injecting ERELZI Using a Prefilled Syringe

Only remove the needle cap when you are ready to use the ERELZI prefilled syringe.

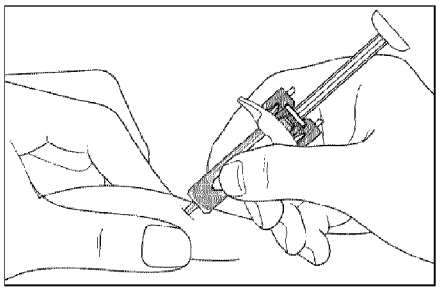
1. Carefully remove the needle cap from the ERELZI prefilled syringe (**see Figure G**). Throw away the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

Figure G



2. With one hand gently pinch the skin at the injection site. With your other hand insert the needle into your skin as shown **(see Figure H)**. Push the needle all the way in to make sure that you inject your full dose.

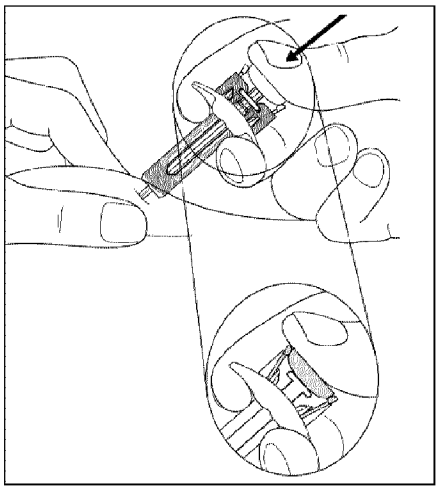
Figure H



3. Hold the ERELZI prefilled syringe as shown **(see Figure I)**. Slowly press down on the plunger as far as it will go, so that the plunger head is completely between the needle guard wings.

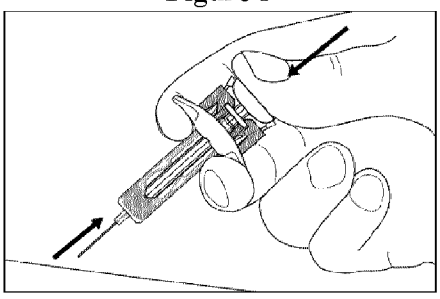
4. Keep the plunger fully pressed down while you hold the syringe in place for 5 seconds.

Figure I



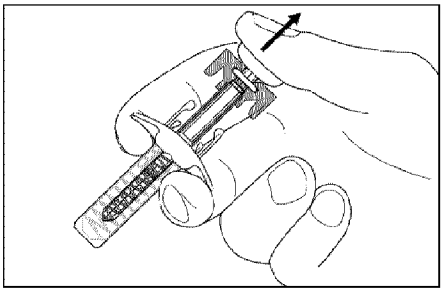
5. Keep the plunger fully pressed down while you carefully pull the needle straight out from the injection site **(see Figure J).**

Figure J



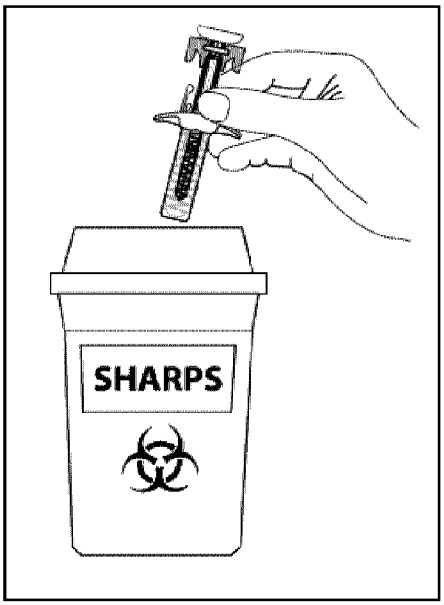
6. Slowly release the plunger and allow the needle guard to automatically cover the exposed needle **(see Figure K).**
7. There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Figure K



How should I throw away used ERELZI prefilled syringes?

Figure L



Put your used prefilled syringes in an FDA-cleared sharps disposal container right away after use **(see Figure L). Do not throw away (dispose of)** ERELZI prefilled syringes in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and prefilled syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Sandoz Inc.

Princeton, NJ 08540

US License No. 2003

At:

Novartis Pharma AG

Stein, Switzerland

Product of Austria

Issued: 08 2016

EXHBIT E
REDACTED
IN FULL

EXHBIT F
REDACTED
IN FULL

EXHBIT G
REDACTED
IN FULL

EXHBIT H
REDACTED
IN FULL

EXHBIT I

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IMMUNEX CORPORATION; AMGEN MANUFACTURING, LIMITED; and HOFFMANN-LA ROCHE INC.;	)	Civil Action No.: 2:16-cv-01118-CCC-MF
Plaintiffs,	)	
v.	)	
SANDOZ INC.; SANDOZ INTERNATIONAL GMBH; and SANDOZ GMBH;	)	**JOINT CLAIM CONSTRUCTION AND PREHEARING STATEMENT PURSUANT TO L. PAT. R. 4.3**
Defendants.	)	

Pursuant to Local Patent Rule 4.3 and the Court's Pretrial Scheduling Order (Dkt. No. 97), the parties submit this Joint Claim Construction and Prehearing Statement regarding disputed terms in United States Patent Nos. 8,063,182 ("the '182 patent"); 8,163,522 ("the '522 patent"); 7,915,225 ("the '225 patent"); 8,119,605 ("the '605 patent"); and 8,722,631 ("the '631 patent") (collectively, "the patents-in-suit").

I. Background

This is a patent infringement action under 35 U.S.C. § 271, including § 271(e)(2)(C), which was enacted in 2010 as part of the Biologics Price Competition and Innovation Act ("BPCIA"). Plaintiffs Immunex Corporation and Amgen Manufacturing, Limited (collectively, "Immunex") manufacture and market the biologic drug product Enbrel®. Immunex Corporation owns the '225, '605, and '631 patents and is the exclusive licensee to the '182 and '522 patents, which are owned by plaintiff Hoffmann-La Roche Inc. ("Roche"). Amgen Manufacturing Limited is the exclusive licensee to the '225, '605, and '631 patents and is the exclusive sublicensee to the '182 and '522 patents.

Plaintiffs allege that defendants Sandoz, Inc., Sandoz International GmbH, and Sandoz GmbH (collectively, "Defendants"[1]) have infringed the asserted claims of the '182 and '522 patents by filing an abbreviated Biologics License Application ("aBLA") pursuant to the BPCIA, seeking authorization from the FDA to market a biosimilar version of Enbrel®. Plaintiffs also allege that Defendants will infringe the asserted claims of the '182 and '522 patents if allowed to market their biosimilar version of Enbrel®.

Immunex alleges that Defendants have infringed the asserted claims of the '225, '605, and '631 patents by filing an aBLA pursuant to the BPCIA, seeking authorization from the FDA

[1] At present, Sandoz, Inc. and Sandoz International GmbH have answered Plaintiffs' Complaint. *See* ECF 31, 106. Sandoz GmbH was recently served.

to market a biosimilar version of Enbrel®. Immunex also alleges that Defendants will induce infringement of the asserted claims of the '225, '605, and '631 patents if allowed to market their biosimilar version of Enbrel®.

Sandoz alleges that the all of the patents-in-suit are invalid and that the '182 and '522 patents also are unenforceable. Sandoz also alleges that it does not infringe at least certain claims of the patents-in-suit.

II. Local Patent Rule 4.3

A. Agreed Constructions

Immunex and Sandoz have agreed to the construction of claim terms as set forth below.

Term / Claims	Asserted Claims	Agreed Construction
"therapeutically effective dose"	'225 claims 1-9, 12-15 '605 claims 1-4, 10-13	Plain and ordinary meaning: "an amount suitable for therapy"
"wherein (a) a dose of 50 mg of TNFR:Fc is administered two times per week for at least two months and then (b) TNFR:Fc is administered at a reduced dose or a reduced frequency"	'225 claims 5-8 '605 claims 10-13	Plain and ordinary meaning: "wherein (a) a dose of 50 mg of etanercept is administered two times per week for at least two months and then (b) etanercept is administered at a reduced dose or at a reduced frequency"
"(a) administering to the patient TNFR:Fc subcutaneously at a dose of 50 mg twice per week for at least two months, and then (b) administering TNFR:Fc subcutaneously at a dose of 50 mg once per week or at a dose of 25 mg twice per week"	'225 claims 16, 20	Plain and ordinary meaning: "(a) administering to the patient etanercept subcutaneously at a dose of 50 mg twice per week for at least two months, and then (b) administering etanercept subcutaneously at a dose of 50 mg once per week or at a dose of 25 mg twice per week"

B. Disputed Terms

Immunex and Sandoz dispute the proper construction of the terms set forth below. Pursuant to L. Pat. R. 4.3(b), attached to this statement as Exhibits A and B are charts in which the parties have set forth their respective proposed construction of each disputed term, together with an identification of all intrinsic and extrinsic evidence that each party intends to rely upon either to support its proposed construction or to oppose the other party's proposed construction.

1. Terms applicable to the '182 and '522 patents

Term / Claims	Asserted Claims	Immunex's Proposal	Sandoz's Proposal
"all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain of said constant region"[2] "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region"	'182 claims 1-36 '522 claims 1-3, 7-10	Plain and ordinary meaning: "'-hinge-CH2-CH3' region of a human [IgG/IgG1]"	"the CH2 and CH3 domains of human [IgG/IgG1]"
"the extracellular region of the insoluble human	'182 claims 11, 35	Plain and ordinary meaning:	"the extracellular region of the p75 TNFR,

[2] Variations of this term that appear in the claim language include: "all of the domains of the constant region of a human IgG1 heavy chain other than the first domain of the constant region"; "all of the domains of the constant region of the human IgG1 heavy chain other than the first domain of the constant region"; "all of the domains of the constant region of the heavy chain of a human IgG immunoglobulin other than the first domain of said constant region"; "all the domains of the constant region of the human immunoglobulin IgG heavy chain other than the first domain of said constant region"; "all the domains of the constant region of a human IgG1 immunoglobulin heavy chain other than the first domain of the constant region"; and "all of the domains of the constant region of the human immunoglobulin IgG heavy chain other than the first domain of the constant region." The parties agree that all variations of this term should have the same construction as that proposed by each party for this term (with alternative bracketed language being logically applied in context for the IgG and IgG1 variations).

Term / Claims	Asserted Claims	Immunex's Proposal	Sandoz's Proposal
TNF receptor" "the extracellular region of the human tumor necrosis factor (TNF) receptor"		"that portion of the human [75 kDa] TNF receptor that protrudes outside the cell"	consisting of amino acids 23-257 of the amino acid sequence of SEQ ID NO: 27"
"the extracellular region of the human tumor necrosis factor (TNF) receptor, wherein the insoluble human TNF receptor has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel and comprises the amino acid sequence LPAQVAFXPYAPEP GSTC (SEQ ID NO: 10)"	'522 claims 1-3		
"the extracellular region of an insoluble human TNF receptor, wherein the insoluble human TNF receptor comprises the amino acid sequence of SEQ ID NO: 27"[3]	'522 claims 7-10		
"specifically binds human TNF"	'182 claims 1-36	Plain and ordinary meaning: "has the ability to strongly and stably bind human TNF"	"binds a detectable amount of TNF in an *in vitro* TNF-binding assay"

[3] Sandoz asserts that all four variations should have the same construction. Immunex asserts that all variations should share the non-bracketed language Immunex proposes, but that only the last two variations contextually merit the further inclusion of the additional bracketed language.

Term / Claims	Asserted Claims	Immunex's Proposal	Sandoz's Proposal
"wherein the polynucleotide encodes a protein consisting of"	'522 claims 1-3, 7-10	Plain and ordinary meaning: "wherein the polynucleotide contains the genetic information for a protein consisting of"	"the polynucleotide encodes only the protein and includes no other amino acid sequence"

For the Court's convenience, exemplary claims are shown below in their entirety with the disputed claim terms underlined.

Independent claim 1 of the '182 patent recites:

> 1. A protein comprising
>
> (a) a human tumor necrosis factor (TNF)-binding soluble fragment of an insoluble human TNF receptor, wherein the insoluble human TNF receptor (i) specifically binds human TNF, (ii) has an apparent molecular weight of about 75 kilodaltons on a non-reducing SDS-polyacrylamide gel, and (iii) comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10); and
>
> (b) all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain of said constant region;
>
> wherein said protein specifically binds human TNF.

Dependent claim 11 of the '182 patent recites:

> 11. The protein of claim 1, wherein the protein consists essentially of the extracellular region of the insoluble human TNF receptor and all the domains of the constant region of a human IgG_1 immunoglobulin heavy chain other than the first domain of the constant region.

Dependent claim 35 of the '182 patent recites:

> 35. The protein of claim 30, wherein the protein consists essentially of the extracellular region of the human tumor necrosis factor (TNF) receptor amino acid sequence encoded by the cDNA insert, and all the domains of the constant region of a human IgG_1

immunoglobulin heavy chain other than the first domain of the constant region.

Independent claim 1 of the ’522 patent recites:

1. A method comprising the steps of:

(a) culturing a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein consisting of:

(i) the extracellular region of an insoluble human TNF receptor, wherein the insoluble human TNF receptor has an apparent molecular weight of about 75 kilodaltons as determined on a non-reducing SDS-polyacrylamide gel and comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), and

(ii) all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region, and

(b) purifying an expression product of the polynucleotide from the cell mass or the culture medium.

Independent claim 7 of the ’522 patent recites:

7. A method comprising the steps of:

(a) culturing a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein consisting of:

(i) the extracellular region of a insoluble human TNF receptor, wherein the insoluble human TNF receptor comprises the amino acid sequence of SEQ ID NO: 27 and

(ii) all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region, and

(b) purifying an expression product of the polynucleotide from the cell mass or culture medium.

2. Terms applicable to the ’225, ’605, and ’631 patents

Term / Claims	Asserted Claims	Immunex’s Proposal	Sandoz’s Proposal
“psoriasis”	’225 claims 1-9, 12-16, 20	Plain and ordinary meaning:	“an inflammatory disease of the skin and/or nails that does not include the

Term / Claims	Asserted Claims	Immunex's Proposal	Sandoz's Proposal
		"a particular human inflammatory disease of the skin, as diagnosed by physicians"	symptoms of psoriatic arthritis" or indefinite under 35 U.S.C. § 112
"psoriatic arthritis"	'225 claims 12-15 '631 claims 1-5, 7, 17-22	Plain and ordinary meaning: "a particular human inflammatory disease of the skin and joints, as diagnosed by physicians"	"an inflammatory disease characterized by one or more swollen joints or one or more painful or tender joints, and also manifest at least one psoriatic lesion of the skin or nails prior to or concurrent with the onset of joint symptoms" or indefinite under 35 U.S.C. § 112
"ordinary psoriasis"	'605 claims 1-4, 10-13	Plain and ordinary meaning: "psoriasis without the more serious symptoms of psoriatic arthritis"	"an inflammatory disease of the skin and/or nails that does not include the symptoms of psoriatic arthritis" or indefinite under 35 U.S.C. § 112.
"plaque psoriasis"	'631 claims 1-6, 8-15	Plain and ordinary meaning: "a subtype of a particular human inflammatory disease of the skin, as diagnosed by physicians, distinguished by skin lesions having silvery white scale"	"an inflammatory disease of the skin characterized by inflamed swollen skin lesions covered with silvery white scale"
"patient"	'225 claims 1-9, 12-16, 20 '605 claims 1-4, 10-13 '631 claims 1-15, 17-22	Plain and ordinary meaning: "human in need of treatment"	"any animal, including a non-human animal"

For the Court's convenience, exemplary claims are shown below in their entirety with the disputed claim terms underlined.

Independent claim 1 of the ’225 patent recites:

> 1. A method for treating a patient having psoriasis comprising administering to the patient a therapeutically effective dose of TNFR:Fc, wherein the patient attains at least fifty percent improvement in PASI score.

Dependent claim 12 of the ’225 patent recites:

> 12. A method for treating a patient having psoriasis and psoriatic arthritis comprising administering to the patient a therapeutically effective dose of TNFR:Fc, wherein the patient attains at least fifty percent improvement in PASI score.

Independent claim 1 of the ’605 patent recites:

> 1. A method for treating a patient having ordinary psoriasis comprising administering to the patient a therapeutically effective dose of TNFR:Fc.

Independent claim 1 of the ’631 patent recites:

> 1. A method of treatment comprising administering a dose of TNFR:Fc to a patient having psoriatic arthritis and/or plaque psoriasis,
>
> wherein the dose is administered one time or two times per week, and
> wherein the dose administered is 25-50 mg or 50-100 mg, and
> wherein the dose is administered by subcutaneous injection.

C. Identification of Significant Terms

Pursuant to L. Pat. R. 4.3(c), Immunex and Sandoz identify the following terms “whose construction will be most significant to the resolution of the case” or “whose construction will be case or claim dispositive or substantially conducive to promoting settlement.” While Immunex and Sandoz recognize that the exclusive adoption by the Court of each and every proposal put forth by one side or the other would have a significant impact on the parties’ preparation of their cases for trial and appeal, they do not consider the resolution of any particular term or terms to be either case dispositive or substantially conducive to settlement.

D. Anticipated Length of Time for Claim Construction Hearing

Pursuant to L. Pat. R. 4.3(d), Immunex and Sandoz estimate that the entire claim construction hearing will be conducted in no more than one day. They further agree that each shall have equal aggregate argument time. The parties will not present a separate or preliminary technology tutorial and, instead, will incorporate relevant technical background into their respective arguments.

E. Identification of Witnesses for the Claim Construction Hearing

Pursuant to L. Pat. R. 4.3(e), the parties will not present live expert testimony unless the Court requests it in advance with regard to specific issues set forth in the parties' disclosures of expert opinion in Exhibits A and B.

Date: Oct. 17, 2016

Respectfully submitted,

s/Liza M. Walsh

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CERTIFICATE OF SERVICE

The undersigned attorney certifies that a copy of the foregoing JOINT CLAIM CONSTRUCTION AND PREHEARING STATEMENT PURSUANT TO L. PAT. R. 4.3 was served by electronic mail on all counsel of record.

Dated: Oct. 17, 2016

s/Liza M. Walsh

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July 10, 2016

VIA EMAIL
Jeffrey P. Kushan
Sidley Austin LLP
1501 K Street NW
Washington, DC 20005-1401

Dear Jeff,

As you know, Sandoz has filed an application for FDA approval of a Sandoz biosimilar etanercept product, for which Immunex's ENBREL® is the reference product. Sandoz will have a FDA Advisory Committee meeting on July 13, 2016 and expects – based in part on communications from the FDA – to receive FDA approval to market its product on August 30, 2016. Absent some agreement between the parties, Sandoz intends to begin commercial marketing of its product immediately thereafter.

Sandoz is aware of the prevailing Federal Circuit precedent requiring the provision of a "notice of commercial marketing" to be provided pursuant to 42 U.S.C. § 262(*l*)(8)(A), that such notice can only be provided at FDA approval, and that such notice is mandatory. However, those judgments are the subject of a Supreme Court petition, and may yet be the subject of a further petition on request for en banc review. Further, we recognize that, should the Supreme Court accept our client's petition, any decision is only likely to be given in the first half of 2017. In this letter, Sandoz seeks to preserves its entitlement to damages should the courts ultimately determine that notice can be given prior to approval, or that notice is not mandatory.

To that end, Sandoz gives the following notices:

(1) Solely to preserve Sandoz's potential future entitlement to damages, in the event that the Supreme Court ultimately rules that Sandoz is not required to wait until FDA approval of its etanercept product before providing its notice of commercial marketing under 42 U.S.C. § 262(*l*)(8)(A) or that that notice is not mandatory, this letter serves as notice that Sandoz intends to commercially market its product no later than 180 days **from today**.

(2) If the Supreme Court ultimately rules that Sandoz is required to wait until FDA approval before providing its § 262(*l*)(8)(A) notice and that such notice is mandatory,

this letter serves as notice that Sandoz intends to commercially market its product no later than 180 days from the day it receives FDA approval for its etanercept product, such notice **only becoming effective on FDA approval**.

Accordingly, Sandoz provides such notice without waiving its right to begin commercial marketing at any time after receiving approval and without waiving any argument that it is not or should not be required to: (1) provide the notice as set forth in § 262(*l*)(8)(A) or (2) provide that notice only after FDA approval.

Please note that if your clients are of the view that the notice referred to in paragraph (2) above does not satisfy the requirements of 42 U.S.C. § 262(*l*)(8)(A) as currently interpreted by the Federal Circuit in *Amgen v. Sandoz* and *Amgen v. Apotex*, please advise by no later than July 31, 2016.

Best regards,

Maureen L. Rurka

EXHBIT K

U 7574173

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 10, 2016

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *8,722,631*
ISSUE DATE: *May 13, 2014*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

T. Lawrence

T. LAWRENCE
Certifying Officer


US008722631B2

(12) **United States Patent**
Finck

(10) **Patent No.: US 8,722,631 B2**
(45) **Date of Patent: *May 13, 2014**

(54) **SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR TREATMENT OF MEDICAL DISORDERS**

(71) Applicant: **Immunex Corporation**, Thousand Oaks, CA (US)

(72) Inventor: **Barbara K. Finck**, San Francisco, CA (US)

(73) Assignee: **Immunex Corporation**, Thousand Oaks, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/773,319**

(22) Filed: **Feb. 21, 2013**

(65) **Prior Publication Data**

US 2013/0164287 A1 Jun. 27, 2013

Related U.S. Application Data

(60) Division of application No. 13/367,071, filed on Feb. 6, 2012, now Pat. No. 8,410,060, which is a division of application No. 13/021,545, filed on Feb. 4, 2011, now Pat. No. 8,119,605, which is a continuation of application No. 12/394,962, filed on Feb. 27, 2009, now Pat. No. 7,915,225, which is a division of application No. 10/853,479, filed on May 25, 2004, now abandoned, which is a division of application No. 09/602,351, filed on Jun. 23, 2000, now abandoned, and a continuation-in-part of application No. 09/378,828, filed on Aug. 13, 1999, now abandoned.

(60) Provisional application No. 60/164,676, filed on Nov. 10, 1999, provisional application No. 60/184,864, filed on Feb. 25, 2000, provisional application No. 60/130,074, filed on Apr. 19, 1999, provisional application No. 60/134,320, filed on May 14, 1999, provisional application No. 60/143,959, filed on Jul. 15, 1999, provisional application No. 60/148,234, filed on Aug. 11, 1999.

(51) **Int. Cl.**

A61K 38/16	(2006.01)
C07K 14/475	(2006.01)
C07K 14/525	(2006.01)

(52) **U.S. Cl.**

USPC **514/21.2**; 514/18.7; 514/169; 552/588; 607/94; 530/350; 530/866

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The invention pertains to methods and compositions for treating medical disorders characterized by elevated levels or abnormal expression of TNFα by administering a TNFα antagonist, such as recombinant TNFR:Fc.

22 Claims, No Drawings

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Office Action, U.S. Appl. No. 13/367,071, mailed Mar. 20, 2012.

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SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR TREATMENT OF MEDICAL DISORDERS

This application is a divisional of U.S. application Ser. No. 13/367,071, filed Feb. 6, 2012, now allowed; which is a divisional of U.S. application Ser. No. 13/021,545, filed Feb. 4, 2011, now U.S. Pat. No. 8,119,605; which is a continuation of U.S. application Ser. No. 12/394,962, filed Feb. 27, 2009, now U.S. Pat. No. 7,915,225; which is a divisional of U.S. application Ser. No. 10/853,479, filed May 25, 2004, now abandoned; which is a divisional of U.S. application Ser. No. 09/602,351, filed Jun. 23, 2000, now abandoned, which claims benefit of U.S. Provisional Application Nos. 60/164,676, filed Nov. 10, 1999, now abandoned, and 60/184,864, filed Feb. 25, 2000, now abandoned; and which is a continuation-in-part of U.S. application Ser. No. 09/373,828, filed Aug. 13, 1999, now abandoned, which claims the benefit of U.S. Provisional Application Nos. 60/130,074, filed Apr. 19, 1999, now abandoned, 60/134,320, filed May 14, 1999, now abandoned, 60/143,959, filed Jul. 15, 1999, now abandoned, and 60/148,234, filed Aug. 11, 1999, now abandoned; all of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention pertains to methods for treating various medical disorders that are characterized by abnormal or excessive TNFα levels by administering a TNFα antagonist, preferably a soluble TNFα. The TNFα inhibitor may be administered in combination with other biologically active molecules.

BACKGROUND OF THE INVENTION

The pleiotropic cytokine tumor necrosis factor alpha (TNFα) is associated with inflammation and binds to cells through membrane receptor molecules, including two molecules having molecular weights of approximately 55 kDa and 75 kDa (p55 and p75). In addition to binding TNFα, the p55 and p75 TNF receptors mediate the binding to cells of homotrimers of TNFβ, which is another cytokine associated with inflammation and which shares structural similarities with TNFα (e.g., see Cosman, *Blood Cell Biochem* 7:51-77, 1996). TNFβ is also known as lymphotoxin-α (LTα).

It has been proposed that a systemic or localized excess of TNFα contributes to the progression of numerous medical disorders. For example, patients with chronic heart failure have elevated levels of serum TNFα, which have been shown to increase with disease progression (see, for example, Levine et al., *N Eng J Med* 323:236-241, 1990). A variety of other diseases are associated with elevated levels of TNFα (see, for example, Feldman et al., *Transplantation Proceedings* 30:4126-4127, 1998).

Psoriatic arthritis (PsA) is a chronic autoimmune condition that shares some features with both rheumatoid arthritis (RA) and the inflammatory skin disease psoriasis (for review, see Breathnach, In Klippel and Dieppe eds. *Rheumatology*, 2nd Ed., Mosby, 1998, 22.1-22.4). Psoriasis is characterized by epidermal keratinocyte hyperproliferation, accompanied by neutrophil and T cell infiltration, and is associated with elevated levels of inflammatory cytokines, including TNFα, IL-6 and TGFβ (see, for example, Bonifati et al., *Clin Exp Dermatol* 19:383-387, 1994). Psoriasis and PsA are different clinical entities, and are associated with somewhat different MHC haplotypes (Gladman, *Rheum Dis Clin NA.* 18:247-256, 1992; Breathnach, 1998). The overall prognosis for PsA is far worse than for ordinary psoriasis. Nonetheless, treatments used for the psoriatic lesions of PsA generally are similar to those used to treat psoriasis.

Psoriatic skin lesions are present in patients with PsA, although only a minority of psoriasis sufferers actually have PsA. Ordinary psoriasis occasionally is accompanied by joint pain, but does not involve the extreme pain and often deforming degeneration of joints and bone that occurs in PsA patients.

Treatments that sometimes are effective in treating ordinary psoriasis include topical medications (e.g., steroids, coal tar, anthralin, Dead Sea salts, various natural oils, vitamin D3 and its analogs, sunshine, topical retinoids), phototherapy (e.g., ultraviolet light, photochemotherapy (PUVA)), and internal medications (e.g., methotrexate, systemic steroids, oral retinoids, cyclosporine, or a rotating regimen of these three). In addition, it has been proposed that psoriasis could be treated with TNF-derived peptides, quinolinesulfonamides, pyrrolidinone derivatives, catechol diether compounds, isoxazoline compounds, matrix metalloproteinase inhibitors or mercapto alkyl peptidyl compounds, all of which inhibit either TNFα production or its release from cultured cells (see, for example, U.S. Pat. No. 5,691,382, U.S. Pat. No. 5,834,485, U.S. Pat. No. 5,420,154, U.S. Pat. No. 5,563,143, U.S. Pat. No. 5,869,511 and U.S. Pat. No. 5,872,146), as well as with various combination therapies involving TNFα antagonists (for example, see U.S. Pat. No. 5,888,511 or U.S. Pat. No. 5,958,413).

Conflicting results have been reported regarding the role of TNFα in psoriasis. Some investigators have proposed that overproduction of TNFα contributes to the pathology of psoriasis (e.g., Pigatto et al., *J Invest Dermatol* 94:372-376, 1990; Sagawa et al., *Dermatol* 187:81-83, 1993; Ameglio et al., *Dermatol* 189:359-363, 1994). One group reported some improvement after treatment with pentoxifylline, a drug that can inhibit the release of TNFα, but which exerts many of its physiological effects by inhibiting cyclic AMP phosphodiesterase (Omulecki et al., *J Am Acad Dermatol* 34:714-715, 1996; Centola et al., *J Androl* 16:136-142, 1995; Elferinck et al., *Biochem Pharmacol* 54:475-480, 1997). However, other reports have cast doubt on the hypothesis that overproduction of TNFα exacerbates psoriasis. For example, some investigators have reported that treatment with TNFα itself actually can mitigate psoriasis (see, e.g., Takematsu et al., *Br J Dermatol* 124:209-210, 1991; Creaven et al., *J Am Acad Dermatol* 24:735-737, 1991).

In addition to psoriatic lesions, PsA is characterized by distal interphalangeal joint (DIP) involvement, enthesopathy, nail lesions, spondylitis and dactylitis. The histopathogenesis of PsA and the more well-studied rheumatoid arthritis share certain features. In both RA and in active PsA, patients exhibit increased levels of HLA-DR$^+$ T cells and MHC class II antigens in their synovial membranes and synovial fluid, as well as increased expression of the cytokine TNFα. In addition, both diseases are associated with prominent synovial vascular changes.

The discovery of rheumatoid factor in the serum of RA patients provided an important tool for differentiating PsA from RA, but the realization that RA and PsA are distinct diseases was based primarily on their many clinical differences (e.g., Helliwell and Wright, In Klippel and Dieppe eds. *Rheumatology*, 2nd Ed., Mosby, 1998, 21.1-21.8). Studies have shown that levels of TNFα, Il-1β, Il-8 as well as TNFα receptors in synovial fluids were higher in PsA patients than in osteoarthritis patients, though they were lower than in RA patients (Partsch et al., *J Rheumatol* 24:518-523, 1997; Partsch et al., *J Rheumatol* 25:105-110, 1998; Partsch et al.,

Ann Rheum Dis 57:691-693, 1998). PsA is distinguished from RA also by radiographic appearance, a notably higher degree of synovial membrane vascularity as well as differences in the levels of various cytokines in the synovial fluids (Ritchlin et al., *J Rheumatol* 25:1544-52, 1998; Veale et al., *Arth Rheum* 36:893-900, 1993). Veale et al. noted differences in synovial membrane adhesion molecules and numbers of macrophages when they compared RA and PsA patients, as well as observing a minimal degree of hyperplasia and hypertrophy of synoviocytes in PsA as compared with RA patients. Because of such differences, coupled with the association of PsA but not RA with class I MHC antigens, Ritchlin et al. have suggested that PsA must be triggered by different mechanisms than those underlying RA. Veale et al. suggested for similar reasons that different cytokines were likely to be interacting in the synovium of PsA and RA patients.

Most of the drugs used for treating the arthritic aspects of PsA are similar to those used in RA (Salvarini et al., *Curr Opin Rheumatol* 10:229-305, 1998), for example the non-steroidal antiinflammatories (NSAIDs), which may be used alone or in combination with the disease-modifying anti-rheumatic drugs, or "DMARDs." However, one group found that long-term administration of the DMARD methotrexate failed to slow the progression of joint damage in PsA patients (Abu-Shakra et al., *J Rheumatol* 22:241-45, 1995), and another group reported very little improvement in PsA patients who had received methotrexate (Willkens et al., *Arthr Rheum* 27:376-381, 1984). Similarly, Clegg et al. found only a slight improvement over placebo in PsA patients treated with sulfasalazine, another drug classified as a DMARD (Clegg et al., *Arthritis Rheum* 39: 2013-20, 1996). Some studies have indicated that the immunosuppressor cyclosporine is effective in treating PsA (reviewed in Salvarini et al., 1998), though this drug has severe side effects. In addition, others have proposed that PsA could be treated with truncated TNFα receptors or with a combination of methotrexate and antibodies against TNFα (WO 98/01555; WO 98/0537).

A recent meta-analysis of a number of PsA treatment studies concluded that PsA and RA differed not only in their response to treatment with specific drugs, but in the relative magnitudes of improvement in the placebo arms of the studies (Jones et al., *Br J Rheumatol* 36:95-99, 1997). As an example, PsA patients responded better to gold salt therapy than did RA patients, though the gold did not affect the psoriatic skin lesions (Dorwart et al., *Arthritis Rheum* 21:515-513, 1978).

It has been suggested that the suppression of TNFα might be beneficial in patients suffering from various disorders characterized by abnormal or excessive TNFα expression. However, although progress has been made in devising effective treatment for such diseases, improved medicaments and methods of treatment are needed.

SUMMARY OF THE INVENTION

Provided herein are methods for treating a number of medical disorders characterized by abnormal TNFα expression by repeatedly administering an antagonist of TNFα, such as a soluble TNFα receptor, for a period of time sufficient to induce a sustained improvement in the patient's condition.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides compounds, compositions and methods for treating a mammalian patient, including a human patient, who is suffering from a medical disorder that is characterized by abnormal or elevated expression of TNFα. For purposes of this disclosure, the terms "illness," "disease," "medical condition," "abnormal condition" and the like are used interchangeably with the term "medical disorder."

The subject methods involve administering to the patient a soluble TNFα antagonist that is capable of reducing the effective amount of endogenous biologically active TNFα, such as by reducing the amount of TNFα produced, or by preventing the binding of TNFα to its cell surface receptor (TNFR). Antagonists capable of inhibiting this binding include receptor-binding peptide fragments of TNFα, antibodies directed against TNFα, and recombinant proteins comprising all or portions of receptors for TNFα or modified variants thereof, including genetically-modified muteins, multimeric forms and sustained-release formulations. Other compounds suitable for treating the diseases described herein include thalidomide and pentoxifylline.

Preferred embodiments of the invention utilize soluble TNFRs as the TNFα antagonist. Soluble forms of TNFRs may include monomers, fusion proteins (also called "chimeric proteins), dimers, trimers or higher order multimers. In certain embodiments of the invention, the soluble TNFR derivative is one that mimics the 75 kDa TNFR or the 55 kDa TNFR and that binds to TNFα in the patient's body. The soluble TNFR mimics of the present invention may be derived from TNFRs p55 or p75 or fragments thereof. TNFRs other than p55 and p75 also are useful for deriving soluble compounds for treating the various medical disorders described herein, such for example the TNFR described in WO 99/04001. Soluble TNFR molecules used to construct TNFR mimics include, for example, analogs or fragments of native TNFRs having at least 20 amino acids, that lack the transmembrane region of the native TNFR, and that are capable of binding TNFα. Antagonists derived from TNFRs compete for TNFα with the receptors on the cell surface, thus inhibiting TNFα from binding to cells, thereby preventing it from manifesting its biological activities. Binding of soluble TNFRs to TNFα or LTα can be assayed using ELISA or any other convenient assay. This invention provides for the use of soluble TNFα receptors in the manufacture of medicaments for the treatment of numerous diseases.

The soluble TNFR polypeptides or fragments of the invention may be fused with a second polypeptide to form a chimeric protein. The second polypeptide may promote the spontaneous formation by the chimeric protein of a dimer, trimer or higher order muimer that is capable of binding a TNFα and/or LTα molecule and preventing it from binding to cell-bound receptors. Chimeric proteins used as antagonists include, for example, molecules derived from an antibody molecule and a TNFR. Such molecules are referred to herein as TNFR-Ig fusion proteins. A preferred TNFR-Ig fusion protein suitable for treating diseases in humans and other mammals is recombinant TNFR:Fc, a term which as used herein refers to "etanercept," which is a dimer of two molecules of the extracellular portion of the p75 TNFα receptor, each molecule consisting of a 235 amino acid TNFR-derived polypeptide that is fused to a 232 amino acid Fc portion of human IgG_1. Etanercept is currently sold by Immunex Corporation under the trade name ENBREL.® Because the p75 receptor protein that it incorporates binds not only to TNFα, but also to the inflammatory cytokine LTα, etanercept can act as a competitive inhibitor not only of TNFα, but also of LTα. This is in contrast to antibodies directed against TNFα, which cannot inhibit LTα. Also encompassed by the invention are treatments using a compound that comprises the extracellular portion of the 55 kDa TNFR fused to the Fc portion of IgG, as well as compositions and combinations containing such a molecule. Encompassed also are therapeutic methods involv-

ing the administration of TNFR-Ig proteins derived the extracellular regions of TNFα receptor molecules other than the p55 and p75 TNFRs, such as for example the TNFR described in WO 99/04001.

In one preferred embodiment of the invention, sustained-release forms of soluble TNFRs are used, including sustained-release forms of TNFR:Fc. Sustained-release forms suitable for use in the disclosed methods include, but are not limited to, TNFRs that are encapsulated in a slowly-dissolving biocompatible polymer (such as the alginate microparticles described in U.S. Pat. No. 6,036,978), admixed with such a polymer (including topically applied hydrogels), and or encased in a biocompatible semi-permeable implant. In addition, the soluble TNFR may be conjugated with polyethylene glycol (pegylated) to prolong its serum half-life or to enhance protein delivery.

In accord with this invention, medical disorders characterized by abnormal or excess expression of TNFα are administered a therapeutically effective amount of a TNFα inhibitor. The TNFα inhibitor may be a TNFα-binding soluble TNFα receptor, preferably TNFR:Fc. As used herein, the phrase "administering a therapeutically effective amount" of a therapeutic agent means that the patient is treated with the agent in an amount and for a time sufficient to induce a sustained improvement in at least one indicator that reflects the severity of the disorder. An improvement is considered "sustained" if the patient exhibits the improvement on at least two occasions separated by one or more weeks. The degree of improvement is determined based on signs or symptoms, and determinations may also employ questionnaires that are administered to the patient, such as quality-of-life questionnaires.

Various indicators that reflect the extent of the patient's illness may be assessed for determining whether the amount and time of the treatment is sufficient. The baseline value for the chosen indicator or indicators is established by examination of the patient prior to administration of the first dose of the etanercept or other TNFα inhibitor. Preferably, the baseline examination is done within about 60 days of administering the first dose. If the TNFα antagonist is being administered to treat acute symptoms, such as for example to treat a traumatic knee injury, the first dose is administered as soon as practically possible after the injury has occurred.

Improvement is induced by administering TNFR:Fc or other TNFα antagonist until the patient manifests an improvement over baseline for the chosen indicator or indicators. In treating chronic conditions, this degree of improvement is obtained by repeatedly administering this medicament over a period of at least a month or more, e.g., for one, two, or three months or longer, or indefinitely. A period of one to six weeks, or even a single dose, often is sufficient for treating acute conditions. For injuries or acute conditions, a single dose may be sufficient.

Although the extent of the patient's illness after treatment may appear improved according to one or more indicators, treatment may be continued indefinitely at the same level or at a reduced dose or frequency. Once treatment has been reduced or discontinued, it later may be resumed at the original level if symptoms should reappear.

Any efficacious route of administration may be used to therapeutically administer TNFR:Fc or other TNFα antagonists. If injected, TNFR:Fc can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes by bolus injection or by continuous infusion. Other suitable means of administration include sustained release from implants, aerosol inhalation, eyedrops, oral preparations, including pills, syrups, lozenges or chewing gum, and topical preparations such as lotions, gels, sprays, ointments or other suitable techniques. Alternatively, proteinaceous TNFα inhibitors, such as a soluble TNFR, may be administered by implanting cultured cells that express the protein, for example, by implanting cells that express TNFR:Fc. In one embodiment, the patient's own cells are induced to produce TNFR:Fc by transfection in vivo or ex vivo with a DNA that encodes TNFR:Fc. This DNA can be introduced into the patient's cells, for example, by injecting naked DNA or liposome-encapsulated DNA that encodes TNFR:Fc, or by other means of transfection. When TNFR:Fc is administered in combination with one or more other biologically active compounds, these may be administered by the same or by different routes, and may be administered simultaneously, separately or sequentially.

TNFR:Fc or other soluble TNFRs preferably are administered in the form of a physiologically acceptable composition comprising purified recombinant protein in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers are nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the TNFα antagonist with buffers, antioxidants such as ascorbic acid, low molecular weight polypeptides (such as those having fewer than 10 amino acids), proteins, amino acids, carbohydrates such as glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. In accordance with appropriate industry standards, preservatives may also be added, such as benzyl alcohol. TNFR:Fc preferably is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in standard dosing trials, and may vary according to the chosen route of administration. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the age and condition of the patient, and so forth.

In one embodiment of the invention, TNFR:Fc is administered one time per week to treat the various medical disorders disclosed herein, in another embodiment is administered at least two times per week, and in another embodiment is administered at least three times per week. An adult patient is a person who is 18 years of age or older. If injected, the effective amount of TNFR:Fc per adult dose ranges from 1-20 mg/m^2, and preferably is about 5-12 mg/m^2. Alternatively, a flat dose may be administered, whose amount may range from 5-100 mg/dose. Exemplary dose ranges for a flat dose to be administered by subcutaneous injection are 5-25 mg/dose, 25-50 mg/dose and 50-100 mg/dose. In one embodiment of the invention, the various indications described below are treated by administering a preparation acceptable for injection containing TNFR:Fc at 25 mg/dose, or alternatively, containing 50 mg per dose. The 25 mg or 50 mg dose may be administered repeatedly, particularly for chronic conditions. If a route of administration other than injection is used, the dose is appropriately adjusted in accord with standard medical practices. In many instances, an improvement in a patient's condition will be obtained by injecting a dose of about 25 mg of TNFR:Fc one to three times per week over a period of at least three weeks, or a dose of 50 mg of TNFR:Fc one or two times per week for at least three weeks, though treatment for longer periods may be necessary to induce the desired degree of improvement. For incurable chronic conditions, the regimen may be continued indefinitely, with adjustments being made to dose and frequency if such are deemed necessary by the patient's physician.

For pediatric patients (age 4-17), a suitable regimen involves the subcutaneous injection of 0.4 mg/kg, up to a maximum dose of 25 mg of TNFR:Fc, administered by subcutaneous injection one or more times per week.

The invention further includes the administration of TNFR:Fc concurrently with one or more other drugs that are administered to the same patient in combination with the TNFR:Fc, each drug being administered according to a regimen suitable for that medicament. "Concurrent administration" encompasses simultaneous or sequential treatment with the components of the combination, as well as regimens in which the drugs are alternated, or wherein one component is administered long-term and the other(s) are administered intermittently. Components may be administered in the same or in separate compositions, and by the same or different routes of administration. Examples of drugs to be administered concurrently include but are not limited to antivirals, antibiotics, analgesics, corticosteroids, antagonists of inflammatory cytokines, DMARDs and non-steroidal anti-inflammatories. DMARDs that can be administered in combination with the subject TNFα inhibitors such as TNFR:Fc include azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine sulfate, methotrexate, leflunomide, minocycline, penicillamine, sulfasalazine and gold compounds such as oral gold, gold sodium thiomalate and aurothioglucose. Additionally, TNFR:Fc may be combined with a second TNFα antagonist, including an antibody against TNFα or TNFR, a TNFα-derived peptide that acts as a competitive inhibitor of TNFα (such as those described in U.S. Pat. No. 5,795,859), a TNFR-IgG fusion protein other than etanercept, such as one containing the extracellular portion of the p55 TNFα receptor, a soluble TNFR other than an IgG fusion protein, or other molecules that reduce endogenous TNFα levels, such as inhibitors of the TNFα converting enzyme (see e.g., U.S. Pat. No. 5,594,106). In further embodiments of this invention, TNFR:Fc is administered in combination with pentoxifylline or thalidomide.

If an antibody against TNFα is used as the TNFα inhibitor, a preferred dose range is 0.1 to 20 mg/kg, and more preferably is 1-10 mg/kg. Another preferred dose range for anti-TNFα antibody is 0.75 to 7.5 mg/kg of body weight. Humanized antibodies are preferred, that is, antibodies in which only the antigen-binding portion of the antibody molecule is derived from a non-human source. such antibodies may be injected or administered intravenously.

In one preferred embodiment of the invention, the various medical disorders disclosed herein as being treatable with inhibitors such as TNFR:Fc are treated in combination with another cytokine or cytokine inhibitor. For example, TNFR:Fc may be administered in a composition that also contains a compound that inhibits the interaction of other inflammatory cytokines with their receptors. Examples of cytokine inhibitors used in combination with TNFR:Fc include, for example, antagonists of TGFβ, Il-6 or Il-8. TNFα inhibitors such as TNFR:Fc also may be administered in combination with the cytokines GM-CSF, IL-2 and inhibitors of protein kinase A type 1 to enhance T cell proliferation in HIV-infected patients who are receiving anti-retroviral therapy. Other combinations for treating the hereindescribed diseases include TNFR:Fc administered concurrently with compounds that block the binding of RANK and RANK-ligand, such as antagonistic antibodies against RANK or RANK-ligand, soluble forms of RANK-ligand that do not trigger RANK, osteoprotegerin or soluble forms of RANK, including RANK:Fc. Soluble forms of RANK suitable for these combinations are described, for example, in U.S. Pat. No. 6,017,729. The concurrent administration of TNFR:Fc and RANK:Fc or TNFR:Fc and osteoprotegerin is useful for preventing bone destruction in various settings including but not limited to various rheumatic disorders, osteoporosis, multiple myeloma or other malignancies that cause bone degeneration, or anti-tumor therapy aimed at preventing metastasis to bone, or bone destruction associated with prosthesis wear debris or with periodontitis.

The present invention also relates to the use of the disclosed TNFα inhibitors, such as TNFR:Fc, in the manufacture of a medicament for the prevention or therapeutic treatment of each medical disorder disclosed herein.

The disclosed TNFα inhibitors, compositions and combination therapies described herein are useful in medicines for treating bacterial, viral or protozoal infections, and complications resulting therefrom. One such disease is *Mycoplasma pneumonia*. In addition, provided herein is the use of TNFR:Fc to treat AIDS and related conditions, such as AIDS dementia complex, AIDS associated wasting, lipidistrophy due to antiretroviral therapy; and Kaposi's sarcoma. Provided herein is the use of TNFR:Fc for treating protozoal diseases, including malaria and schistosomiasis. Additionally provided is the use of TNFR:Fc to treat erythema nodosum leprosum; bacterial or viral meningitis; tuberculosis, including pulmonary tuberculosis; and pneumonitis secondary to a bacterial or viral infection. Provided also herein is the use of TNFR:Fc to prepare medicaments for treating louse-borne relapsing fevers, such as that caused by *Borrelia recurrentis*. TNFR:Fc can also be used to prepare a medicament for treating conditions caused by Herpes viruses, such as herpetic stromal keratitis, corneal lesions, and virus-induced corneal disorders. In addition, TNFR:Fc can be used in treating human papillomavirus infections. TNFR:Fc is used also to prepare medicaments to treat influenza.

Cardiovascular disorders are treatable with the disclosed TNFα inhibitors, pharmaceutical compositions or combination therapies, including aortic aneurisms; arteritis; vascular occlusion, including cerebral artery occlusion; complications of coronary by-pass surgery; ischemia/reperfusion injury; heart disease, including atherosclerotic heart disease, myocarditis, including chronic autoimmune myocarditis and viral myocarditis; heart failure, including chronic heart failure (CHF), cachexia of heart failure; myocardial infarction; restenosis after heart surgery; silent myocardial ischemia; post-implantation complications of left ventricular assist devices; Raynaud's phenomena; thrombophlebitis; vasculitis, including Kawasaki's vasculitis; giant cell arteritis, Wegener's granulomatosis; and Schoenlein-Henoch purpura.

TNFα and IL-8 have been implicated as chemotactic factors in atherosclerotic abdominal aortic aneurism (Szekanecz et al., *Pathobiol* 62:134-139 (1994)). Abdominal aortic aneurism may be treated in human patients by administering a soluble TNFR, such as TNFR:Fc, which may be administered in combination with an inhibitor of IL-8, such treatment having the effect of reducing the pathological neovascularization associated with this condition.

A combination of a TNFα inhibitor and one or more other anti-angiogenesis factors may be used to treat solid tumors, thereby reducing the vascularization that nourishes the tumor tissue. Suitable anti-angiogenic factors for such combination therapies include IL-8 inhibitors, angiostatin, endostatin, kringle 5, inhibitors of vascular endothelial growth factor (such as antibodies against vascular endothelial growth factor), angiopoietin-2 or other antagonists of angiopoietin-1, antagonists of platelet-activating factor and antagonists of basic fibroblast growth factor

In addition, the subject TNFα inhibitors, compositions and combination therapies are used to treat chronic pain condi-

tions, such as chronic pelvic pain, including chronic prostatitis/pelvic pain syndrome. As a further example, TNFR:Fc and the compositions and combination therapies of the invention are used to treat post-herpetic pain.

Provided also are methods for using TNFα inhibitors, compositions or combination therapies to treat various disorders of the endocrine system. For example, the TNFα inhibitors are used to treat juvenile onset diabetes (includes autoimmune and insulin-dependent types of diabetes) and also to treat maturity onset diabetes (includes non-insulin dependent and obesity-mediated diabetes). In addition, the subject compounds, compositions and combination therapies are used to treat secondary conditions associated with diabetes, such as diabetic retinopathy, kidney transplant rejection in diabetic patients, obesity-mediated insulin resistance, and renal failure, which itself may be associated with proteinurea and hypertension. Other endocrine disorders also are treatable with these compounds, compositions or combination therapies, including polycystic ovarian disease, X-linked adrenoleukodystrophy, hypothyroidism and thyroiditis, including Hashimoto's thyroiditis (i.e., autoimmune thyroiditis).

Conditions of the gastrointestinal system also are treatable with TNFα inhibitors, compositions or combination therapies, including coeliac disease. In addition, the compounds, compositions and combination therapies of the invention are used to treat Crohn's disease; ulcerative colitis; idiopathic gastroparesis; pancreatitis, including chronic pancreatitis and lung injury associated with acute pancreatitis; and ulcers, including gastric and duodenal ulcers.

Included also are methods for using the subject TNFα inhibitors, compositions or combination therapies for treating disorders of the genitourinary system, such as glomerulonephritis, including autoimmune glomerulonephritis, glomerulonephritis due to exposure to toxins or glomerulonephritis secondary to infections with haemolytic streptococci or other infectious agents. Also treatable with the compounds, compositions and combination therapies of the invention are uremic syndrome and its clinical complications (for example, renal failure, anemia, and hypertrophic cardiomyopathy), including uremic syndrome associated with exposure to environmental toxins, drugs or other causes. Further conditions treatable with the compounds, compositions and combination therapies of the invention are complications of hemodialysis; prostate conditions, including benign prostatic hypertrophy, nonbacterial prostatitis and chronic prostatitis; and complications of hemodialysis.

Also provided herein are methods for using TNFα inhibitors, compositions or combination therapies to treat various hematologic and oncologic disorders. For example, TNFR:Fc is used to treat various forms of cancer, including acute myelogenous leukemia, Epstein-Barr virus-positive nasopharyngeal carcinoma, glioma, colon, stomach, prostate, renal cell, cervical and ovarian cancers, lung cancer (SCLC and NSCLC), including cancer-associated cachexia, fatigue, asthenia, paraneoplastic syndrome of cachexia and hypercalcemia. Additional diseases treatable with the subject TNFα inhibitors, compositions or combination therapies are solid tumors, including sarcoma, osteosarcoma, and carcinoma, such as adenocarcinoma (for example, breast cancer) and squamous cell carcinoma. In addition, the subject compounds, compositions or combination therapies are useful for treating leukemia, including acute myelogenous leukemia, chronic or acute lymphoblastic leukemia and hairy cell leukemia. Other malignancies with invasive metastatic potential can be treated with the subject compounds, compositions and combination therapies, including multiple myeloma. In addition, the disclosed TNFα inhibitors, compositions and combination therapies can be used to treat anemias and hematologic disorders, including anemia of chronic disease, aplastic anemia, including Fanconi's aplastic anemia; idiopathic thrombocytopenic purpura (ITP); myelodysplastic syndromes (including refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation); myelofibrosis/myeloid metaplasia; and sickle cell vasoocclusive crisis.

Various lymphoproliferative disorders also are treatable with the disclosed TNFα inhibitors, compositions or combination therapies. These include, but are not limited to autoimmune lymphoproliferative syndrome (ALPS), chronic lymphoblastic leukemia, hairy cell leukemia, chronic lymphatic leukemia, peripheral T-cell lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, follicular lymphoma, Burkitt's lymphoma, Epstein-Barr virus-positive T cell lymphoma, histiocytic lymphoma, Hodgkin's disease, diffuse aggressive lymphoma, acute lymphatic leukemias, T gamma lymphoproliferative disease, cutaneous B cell lymphoma, cutaneous T cell lymphoma (i.e., mycosis fungoides) and Sézary syndrome.

In addition, the subject TNFα inhibitors, compositions and combination therapies are used to treat hereditary conditions such as Gaucher's disease, Huntington's disease, linear IgA disease, and muscular dystrophy.

Other conditions treatable by the disclosed TNFα inhibitors, compositions and combination therapies include those resulting from injuries to the head or spinal cord, and including subdural hematoma due to trauma to the head.

The disclosed TNFα inhibitors, compositions and combination therapies are further used to treat conditions of the liver such as hepatitis, including acute alcoholic hepatitis, acute drug-induced or viral hepatitis, hepatitis A, B and C, sclerosing cholangitis and inflammation of the liver due to unknown causes.

In addition, the disclosed TNFα inhibitors, compositions and combination therapies are used to treat various disorders that involve hearing loss and that are associated with abnormal TNFα expression. One of these is inner ear or cochlear nerve-associated hearing loss that is thought to result from an autoimmune process, i.e., autoimmune hearing loss. This condition currently is treated with steroids, methotrexate and/or cyclophosphamide, which may be administered concurrently with the TNFR:Fc or other TNFα inhibitor. Also treatable with the disclosed TNFα inhibitors, compositions and combination therapies is cholesteatoma, a middle ear disorder often associated with hearing loss.

In addition, the subject invention provides TNFα inhibitors, compositions and combination therapies for the treatment of non-arthritic medical conditions of the bones and joints. This encompasses osteoclast disorders that lead to bone loss, such as but not limited to osteoporosis, including post-menopausal osteoporosis, periodontitis resulting in tooth loosening or loss, and prosthesis loosening after joint replacement (generally associated with an inflammatory response to wear debris). This latter condition also is called "orthopedic implant osteolysis." Another condition treatable by administering TNFRα inhibitors, such as TNFR:Fc, is temporal mandibular joint dysfunction (TMJ).

A number of pulmonary disorders also can be treated with the disclosed TNFα inhibitors, compositions and combination therapies. One such condition is adult respiratory distress syndrome (ARDS), which is associated with elevated TNFα, and may be triggered by a variety of causes, including exposure to toxic chemicals, pancreatitis, trauma or other causes. The disclosed compounds, compositions and combination

therapies of the invention also are useful for treating bronchopulmonary dysplasia (BPD); lymphangioleiomyomatosis; and chronic fibrotic lung disease of preterm infants. In addition, the compounds, compositions and combination therapies of the invention are used to treat occupational lung diseases, including asbestosis, coal worker's pneumoconiosis, silicosis or similar conditions associated with long-term exposure to fine particles. In other aspects of the invention, the disclosed compounds, compositions and combination therapies are used to treat pulmonary disorders, including chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis or emphysema; fibrotic lung diseases, such as cystic fibrosis, idiopathic pulmonary fibrosis and radiation-induced pulmonary fibrosis; pulmonary sarcoidosis; and allergies, including allergic rhinitis, contact dermatitis, atopic dermatitis and asthma.

Cystic fibrosis is an inherited condition characterized primarily by the accumulation of thick mucus, predisposing the patient to chronic lung infections and obstruction of the pancreas, which results in malabsorption of nutrients and malnutrition. TNFR:Fc may be administered to treat cystic fibrosis. If desired, treatment with TNFR:Fc may be administered concurrently with corticosteroids, mucus-thinning agents such as inhaled recombinant deoxyribonuclease I (such as PULMOZYME®; Genentech, Inc.) or inhaled tobramycin (TOBI®; Pathogenesis, Inc.). TNFR:Fc also may be administered concurrently with corrective gene therapy, drugs that stimulate cystic fibrosis cells to secrete chloride or other yet-to-be-discovered treatments. Sufficiency of treatment may be assessed, for example, by observing a decrease in the number of pathogenic organisms in sputum or lung lavage (such as *Haemophilus influenzae, Stapholococcus aureus*, and *Pseudomonas aeruginosa*), by monitoring the patient for weight gain, by detecting an increase in lung capacity or by any other convenient means.

TNFR:Fc or TNFR:Fc combined with the cytokine IFNγ-1b (such as ACTIMMUNE®; InterMune Pharmaceuticals) may be used for treating cystic fibrosis or fibrotic lung diseases, such as idiopathic pulmonary fibrosis, radiation-induced pulmonary fibrosis and bleomycin-induced pulmonary fibrosis. In addition, this combination is useful for treating other diseases characterized by organ fibrosis, including systemic sclerosis (also called "scleroderma"), which often involves fibrosis of the liver. For treating cystic fibrosis, TNFR:Fc and IFNγ-1b may be combined with PULMOZYME® or TOBI® or other treatments for cystic fibrosis.

TNFR:Fc alone or in combination with IFNγ-1b may be administered together with other treatments presently used for treating fibrotic lung disease. Such additional treatments include glucocorticoids, azathioprine, cyclophosphamide, penicillamine, colchisicine, supplemental oxygen and so forth. Patients with fibrotic lung disease, such as IPF, often present with nonproductive cough, progressive dyspnea, and show a restrictive ventilatory pattern in pulmonary function tests. Chest radiographs reveal fibrotic accumulations in the patient's lungs. When treating fibrotic lung disease in accord with the disclosed methods, sufficiency of treatment may be detected by observing a decrease in the patient's coughing (when cough is present), or by using standard lung function tests to detect improvements in total lung capacity, vital capacity, residual lung volume or by administering a arterial blood gas determination measuring desaturation under exercising conditions, and showing that the patient's lung function has improved according to one or more of these measures. In addition, patient improvement may be determined through chest radiography results showing that the progression of fibrosis in the patient's lungs has become arrested or reduced.

In addition, TNF inhibitors (including soluble TNFRs or antibodies against TNFα or TNFR) are useful for treating organ fibrosis when administered in combination with relaxin, a hormone that down-regulates collagen production thus inhibiting fibrosis, or when given in combination with agents that block the fibrogenic activity of TGF-β. Combination therapies using TNFR:Fc and recombinant human relaxin are useful, for example, for treating systemic sclerosis or fibrotic lung diseases, including cystic fibrosis, idiopathic pulmonary fibrosis, radiation-induced pulmonary fibrosis and bleomycin-induced pulmonary fibrosis.

Other embodiments provide methods for using the disclosed TNFα inhibitors, compositions or combination therapies to treat a variety of rheumatic disorders. These include: adult and juvenile rheumatoid arthritis; systemic lupus erythematosus; gout; osteoarthritis; polymyalgia rheumatica; seronegative spondylarthropathies, including ankylosing spondylitis; and Reiter's disease. The subject TNFα inhibitors, compositions and combination therapies are used also to treat psoriatic arthritis and chronic Lyme arthritis. Also treatable with these compounds, compositions and combination therapies are Still's disease and uveitis associated with rheumatoid arthritis. In addition, the compounds, compositions and combination therapies of the invention are used in treating disorders resulting in inflammation of the voluntary muscle, including dermatomyositis and polymyositis. Moreover, the compounds, compositions ant combinations disclosed herein are useful for treating sporadic inclusion body myositis, as TNFα may play a significant role in the progression of this muscle disease. In addition, the compounds, compositions and combinations disclosed herein are used to treat multicentric reticulohistiocytosis, a disease in which joint destruction and papular nodules of the face and hands are associated with excess production of proinflammatory cytokines by multinucleated giant cells.

For purposes of this invention, patients are defined as having psoriatic arthrisis (PsA) if they have one or more swollen joints or one or more painful or tender joints, and also manifest at least one psoriatic lesion of the skin or nails. The psoriatic lesions may appear before or after the onset of swollen or tender joints. It is understood that prior to treatment, manifestations of PsA may have persisted over time, e.g., for several months or years, and may involve several joints. According to one classification system (reviewed in Alonso et al., 1991), PsA patients can be categorized based on their arthritic symptoms into five clinical subgroups: 1) DIP; 2) mutilans arthritis; 3) symmetrical polyarthritis; 4) oligoarticular arthritis; and 5) ankylosing spondylitis-like. The disclosed therapies, compounds and compositions are suitable for treating all five forms of PsA.

The TNFα inhibitors, compositions and combination therapies of the invention may be used to inhibit hypertrophic scarring, a phenomenon believed to result in part from excessive TNFα secretion. TNF inhibitors may be administered alone or concurrently with other agents that inhibit hypertrophic scarring, such as inhibitors of TGF-α.

Cervicogenic headache is a common form of headache arising from dysfunction in the neck area, and which is associated with elevated levels of TNFα, which are believed to mediate an inflammatory condition that contributes to the patient's discomfort (Martelletti, *Clin Exp Rheumatol* 18(2 Suppl 19):S33-8 (March-April, 2000)). Cervicogenic head-

ache may be treated by administering an inhibitor of TNFα as disclosed herein, thereby reducing the inflammatory response and associated headache pain.

The TNFα inhibitors, compositions and combination therapies of the invention are useful for treating primary amyloidosis. In addition, the secondary amyloidosis that is characteristic of various conditions also are treatable with TNFα inhibitors such as TNFR:Fc, and the compositions and combination therapies described herein. Such conditions include: Alzheimer's disease, secondary reactive amyloidosis; Down's syndrome; and dialysis-associated amyloidosis. Also treatable with the compounds, compositions and combination therapies of the invention are inherited periodic fever syndromes, including familial Mediterranean fever, hyperimmunoglobulin D and periodic fever syndrome and TNF-receptor associated periodic syndromes (TRAPS).

Disorders associated with transplantation also are treatable with the disclosed TNFα inhibitors, compositions or combination therapies, such as graft-versus-host disease, and complications resulting from solid organ transplantation, including transplantion of heart, liver, lung, skin, kidney or other organs. TNFR:Fc may be administered, for example, to prevent or inhibit the development of bronchiolitis obliterans after lung transplantation. Patients undergoing autologous hematopoietic stem cell transplantation in the form of peripheral blood stem cell transplantation may develop "engraftment syndrome," or "ES," which is an adverse and generally self-limited response that occurs about the time of hematopoietic engraftment and which can result in pulmonary deterioration. ES may be treated with inhibitors of either IL-8 or TNFα (such as TNFR:Fc), or with a combination of inhibitors against both of these cytokines.

Ocular disorders also are treatable with the disclosed TNFα inhibitors, compositions or combination therapies, including rhegmatogenous retinal detachment, and inflammatory eye disease, and inflammatory eye disease associated with smoking and macular degeneration.

TNFα inhibitors such as TNFR:Fc and the disclosed compositions and combination therapies also are useful for treating disorders that affect the female reproductive system. Examples include, but are not limited to, multiple implant failure/infertility; fetal loss syndrome or IV embryo loss (spontaneous abortion); preeclamptic pregnancies or eclampsia; and endometriosis.

In addition, the disclosed TNFα inhibitors, compositions and combination therapies are useful for treating obesity, including treatment to bring about a decrease in leptin formation. Also, the compounds, compositions and combination therapies of the invention are used to treat sciatica, symptoms of aging, severe drug reactions (for example, 11-2 toxicity or bleomycin-induced pneumopathy and fibrosis), or to suppress the inflammatory response prior, during or after the transfusion of allogeneic red blood cells in cardiac or other surgery, or in treating a traumatic injury to a limb or joint, such as traumatic knee injury. Various other medical disorders treatable with the disclosed TNFα inhibitors, compositions and combination therapies include; multiple sclerosis; Behcet's syndrome; Sjogren's syndrome; autoimmune hemolytic anemia; beta thalassemia; amyotrophic lateral sclerosis (Lou Gehrig's Disease); Parkinson's disease; and tenosynovitis of unknown cause, as well as various autoimmune disorders or diseases associated with hereditary deficiencies.

The disclosed TNFα inhibitors, compositions and combination therapies furthermore are useful for treating acute polyneuropathy; anorexia nervosa; Bell's palsy; chronic fatigue syndrome; transmissible dementia, including Creutzfeld-Jacob disease; demyelinating neuropathy; Guillain-Barre syndrome; vertebral disc disease; Gulf war syndrome; myasthenia gravis; silent cerebral ischemia; sleep disorders, including narcolepsy and sleep apnea; chronic neuronal degeneration; and stroke, including cerebral ischemic diseases.

Disorders involving the skin or mucous membranes also are treatable using the disclosed TNFα inhibitors, compositions or combination therapies. Such disorders include acantholytic diseases, including Darier's disease, keratosis follicularis and pemphigus vulgaris. Also treatable with the subject TNFα inhibitors, compositions and combination therapies are acne; acne rosacea; alopecia greata; aphthous stomatitis; bullous pemphigoid; burns; eczema; erythema, including erythema multiforme and erythema multiforme bullosum (Stevens-Johnson syndrome); inflammatory skin disease; lichen planus; linear IgA bullous disease (chronic bullous dermatosis of childhood); loss of skin elasticity; mucosal surface ulcers; neutrophilic dermatitis (Sweet's syndrome); pityriasis rubra pilaris; psoriasis; pyoderma gangrenosum; and toxic epidermal necrolysis.

Patients are defined as having ordinary psoriasis if they lack the more serious symptoms of PsA (e.g., distal interphalangeal joint DIP involvement, enthesopathy, spondylitis and dactylitis) but have one of the following: 1) inflamed swollen skin lesions covered with silvery white scale (plaque psoriasis or psoriasis vulgaris); 2) small red dots appearing on the trunk, arms or legs (guttate psoriasis); 3) smooth inflamed lesions without scaling in the flexural surfaces of the skin (inverse psoriasis); 4) widespread reddening and exfoliation of fine scales, with or without itching and swelling (erythrodermic psoriasis); 5) blister-like lesions (pustular psoriasis); 6) elevated inflamed scalp lesions covered by silvery white scales (scalp psoriasis); 7) pitted fingernails, with or without yellowish discoloration, crumbling nails, or inflammation and detachment of the nail from the nail bed (nail psoriasis).

Ordinary psoriasis may be treated by administering to a human patient compositions containing a therapeutically effective amount of a TNFα inhibitor such as a soluble TNF receptor or an antibody against TNFα.

In one preferred embodiment, the therapeutic agent is a soluble TNF receptor, and preferably is a TNFR-Ig. In a preferred embodiment, the TNFR-Ig is TNFR:Fc, which may be administered in the form of a pharmaceutically acceptable composition as described herein. Psoriasis may be treated by administering TNFR:Fc one or more times per week by subcutaneous injection, although other routes of administration may be used if desired. In one exemplary regimen for treating adult human patients, 25 mg of TNFR:Fc is administered by subcutaneous injection two times per week or three times per week for one or more weeks, and preferably for four or more weeks. Alternatively, a dose of 5-12 mg/m^2 or a flat dose of 50 mg is injected subcutaneously one time or two times per week for one or more weeks. In other embodiments, psoriasis is treated with TNFR:Fc in a sustained-release form, such as TNFR:Fc that is encapsulated in a biocompatible polymer, TNFR:Fc that is admixed with a biocompatible polymer (such as topically applied hydrogels), and TNFR:Fc that is encased in a semi-permeable implant.

Various other medicaments used to treat ordinary psoriasis may also be administered concurrently with compositions comprising TNFα inhibitors, such as TNFR:Fc. Such medicaments include: NSAIDs; DMARDs; analgesics; topical steroids; systemic steroids (e.g., prednisone); cytokines; antagonists of inflammatory cytokines; antibodies against T cell surface proteins; anthralin; coal tar; vitamin D3 and its analogs; topical retinoids; oral retinoids; salicylic acid; and hydroxyurea. Suitable analgesics for such combinations

include: acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol. DMARDs suitable for such combinations include: azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine sulfate, methotrexate, leflunomide, minocycline, penicillamine, sulfasalazine, oral gold, gold sodium thiomalate and aurothioglucose. In addition, the TNFR:Fc or other TNFR mimic may be administered in combination with antimalarials or colchicine. NSAIDs suitable for the subject combination treatments of psoriasis include: salicylic acid (aspirin) and salicylate derivatives; ibuprofen; indomethacin; celecoxib; rofecoxib; ketorolac; nambumetone; piroxicam; naproxen; oxaprozin; sulindac; ketoprofen; diclofenac; and other COX-1 and COX-2 inhibitors, propionic acid derivatives, acetic acid derivatives, fumaric acid derivatives, carboxylic acid derivatives, butyric acid derivatives, oxicams, pyrazoles and pyrazolones, including newly developed anti-inflammatories.

If an antagonist against an inflammatory cytokine is administered concurrently with TNFR:Fc to treat psoriasis, suitable targets for such antagonists include TGFβ, Il-6 and Il-8.

In addition, TNFR:Fc may be used to treat psoriasis in combination with topical steroids, systemic steroids, antagonists of inflammatory cytokines, antibodies against T cell surface proteins, anthralin, coal tar, vitamin D3 and its analogs (including 1,25-dihydroxy vitamin D3 and calcipotriene), topical retinoids, oral retinoids (including but not limited to etretinate, acitretin and isotretinoin), topical salicylic acid, methotrexate, cyclosporine, hydroxyurea and sulfasalazine. In addition, TNFR:Fc may be administered to treat psoriasis in combination with one or more of the following compounds; minocycline; misoprostol; oral collagen; 6-mercaptopurine; nitrogen mustard; gabapentin; bromocriptine; somatostatin; peptide T; anti-CD4 monoclonal antibody; fumaric acid; polyunsaturated ethyl ester lipids; zinc; and other drugs that may be used to treat psoriasis. TNFR:Fc may also be used to treat psoriasis in combination with the use of various oils, including fish oils, nut oils and vegetable oils; aloe vera; jojoba; Dead Sea salts; capsaicin; milk thistle; witch hazel; moisturizers; and Epsom salts. In addition, psoriasis may be treated with compositions containing TNFR:Fc in combination with the following therapies: plasmapheresis; phototherapy with ultraviolet light B; psoralen combined with ultraviolet light A (PUVA); and sunbathing.

For determining the sufficiency of treatment when treating ordinary psoriasis in accord with the invention, the TNFR:Fc (or other TNFα inhibitor) is administered in an amount and for a time sufficient to induce an improvement in an indicator such as psoriasis area and severity index (PASI) or an improvement in Target Lesion Assessment score, which is an index for assessing the severity of individual skin lesions. In one embodiment, the treatment is regarded as sufficient when the patient exhibits an at least 50% improvement in his or her PASI score, and in another embodiment, when the patient exhibits an at least 75% improvement in PASI score. The sufficiency of treatment for psoriasis may also be determined by evaluating individual psoriatic lesions for improvement in severity (Psoriasis Target Lesion Assessment Score), and continuing treatment until an improvement is noted according to this scoring system. This scoring system involves determining for an individual lesion whether improvement has occurred in plaque elevation, amount and degree of scaling or degree of erythema, and target lesion response to treatment, each of which is separately scored. Psoriasis Target Lesion Assessment Score is determined by adding together the separate scores for all four of the aforementioned indicia.

In addition to human patients, inhibitors of TNFα are useful in the treatment of autoimmune and inflammatory conditions in non-human animals, such as pets (dogs, cats, birds, primates, etc.), domestic farm animals (horses cattle, sheep, pigs, birds, etc.), or any animal that suffers from a TNFα-mediated inflammatory or arthritic condition. In such instances, an appropriate dose may be determined according to the animal's body weight. For example, a dose of 0.2-1 mg/kg may be used. Alternatively, the dose is determined according to the animal's surface area, an exemplary dose ranging from 0.1-20 mg/m^2, or more preferably, from 5-12 mg/m^2. For small animals, such as dogs or cats, a suitable dose is 0.4 mg/kg. In a preferred embodiment, TNFR:Fc (preferably constructed from genes derived from the same species as the patient), or another soluble TNFR mimic, is administered by injection or other suitable route one or more times per week until the animal's condition is improved, or it may be administered indefinitely.

EXAMPLE

Evaluation of TNFR:Fc in Patients with Psoriatic Arthritis

Sixty patients with active psoriatic arthritis (PsA) were enrolled in a Phase II double-blind, randomized, placebo controlled study to determine whether the subcutaneous biweekly administration of etanercept (recombinant TNFR:Fc) was safe in this patient population and whether efficacy could be documented for both the arthritic and psoriatic aspects of this disease.

In this study, a flat dose of 25 mg of TNFR:Fc was injected subcutaneously two times a week. After 12 weeks, patients who completed the study were eligible for continuation into a 24 week open-label extension of the study, with assessments made at weeks 16, 36 and 30 days post-study. All patients participating in the study extension received etanercept, including those patients who had received placebo during the blinded portion of the study.

In order to qualify for enrollment, subjects had to have at least one of the following forms of PsA: 1) DIP involvement; 2) polyarticular arthritis, absence of rheumatoid nodules and presence of psoriasis; 3) arthritis mutilans; 4) asymmetric peripheral arthritis; or 5) ankylosing spondylitis-like PsA. Subjects furthermore had to exhibit three or more swollen joints and three or more tender or painful joints at the time of enrollment, and to have exhibited an inadequate response to NSAID therapy. Subjects who were on other medications, including methotrexate, NSAIDs or oral corticosteroids were permitted to continue these other treatments at the same dose so long as the investigator considered these other treatments to inadequately control the patient's disease. Methotrexate was concurrently taken by 47% of the etanercept group, and 47% of the placebo group, NSAIDs were concurrently taken by 67% of the etanercept and 77% of the placebos and oral corticosteroids by 40% of the etanercept and 20% of the placebo patients. Pain medications, including acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol, also were permitted during the study, as well as the use of topical tar compounds.

To qualify as having PsA, patients had to have experienced at least one psoriatic lesion of the skin or nails. Patients were evaluated at baseline (day 1 of treatment) as follows: 1) complete joint assessment; 2) psoriasis assessment; 3) duration of morning stiffness; 4) health assessment (quality of life) questionnaire, visual analog scale (HAQ/VAS); 5) patient global

assessment; 6) erythrocyte sedimentation rate (ESR, Westergren); 7) C-reactive protein (CRP); and 8) urinalysis. At weeks 4 and 8, patients were evaluated as follows: 1) complete joint assessment; 2) psoriasis assessment; 3) duration of morning stiffness; 4) HAQ/VAS; 5) patient global assessment. At the end of 12 weeks, subjects were evaluated as follows: 1) complete joint assessment; 2) psoriasis assessment; 3) focused physical exam; 4) duration of morning stiffness; 5) HAQ/VAS; 6) patient global assessment; 6) hematology profile; 7) chemistry profile; 8) ESR; 9) CRP; 10) urinalysis; 11) serum tested for antibody to TNFR:Fc. Only those patients whose psoriasis was stable and covered ≥3% of body area were evaluated for psoriasis response during this trial, although patients whose psoriasis was inactive or covered less area were permitted to enroll.

A primary endpoint for clinical improvement or worsening of PsA was the Psoriatic Arthritis Response score, which is a composite score based on the following four measures: 1) patient self-assessment; 2) physician assessment; 3) joint pain or tenderness; 4) joint swelling. Both self- and physician assessments, i.e., overall assessment of disease status, were measured according to a five point Likert scale, in which a patient was considered as "improved" if his or her score decreased by one category, or as "worse" if his or her score increased by one category. Joint pain or tenderness was measured on a 5-point scale, wherein 1=none and 5=severe (withdrawal on examination). Joint swelling was evaluated on a 4-point scale in which 1=none; 2=mild (detectable synovial thickening without loss of bony contour); 3=moderate (loss of distinctness of bony contours); and 4=severe (bulging synovial proliferation with cystic characteristics). For this last measure, a decrease in swelling of ≥30% was scored as an "improvement," and an increase in swelling of 30% was scored as a "worsening." Patients were classified as "improved" under the Psoriatic Arthritis Response scoring system if they exhibited an improvement in at least two of the four measures described above, provided that one of the improved areas was joint pain or joint tenderness, and where there was no worsening in any of the four measures.

In addition, a secondary endpoint used for assessing psoriatic arthritis was a modified version of the American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis (modified ACR 20 response) (Felson et al., 1995). To qualify as "improved" according to this measure, a patient must have exhibited ≥20% improvement in both tender joint count (78 joints assessed) and swollen joint count (76 joints assessed), and also must have shown an improvement in three of the following five: 1) subject pain assessment; 2) subject global assessment; 3) physician global assessment; 4) subject self-assessed disability; 5) acute-phase reactant (Westergreen erythrocyte sedimentation rate or C-reactive protein level). The joint count was done by scoring several different aspects of tenderness, such as pressure and joint manipulation on physical examination, wherein each joint was scored as "tender" or "nontender." Similarly, each joint is scored after physical examination as "swollen" or "not swollen." The subject's pain assessment was based on a horizontal visual analog scale (usually 10 cm) or Likert scale. The subject's and physician's global assessments of the subject's current disease status was based on an anchored horizontal visual analog scale (usually 10 cm), or Likert scale response. The subject's self-assessment of disability was based on any of the following measures, all of which have been validated in RA trials: Arthritis Impact Measurement Scale (AIMS); Health Assessment Questionnaire; the Quality (or Index) of Well Being Scale; the McMaster Health Inventory Questionnaire (MHIQ); and the McMaster-Toronto Arthritis patient preference questionnaire (MACTAR).

A primary endpoint used to assess the psoriatic aspects of PsA was the standard psoriasis area and severity index (PASI) (Fredriksson and Petersson, *Dermatologica* 157:238-244, 1978). For this study, a positive treatment response was defined as an at least 50% or an at least 75% improvement in a patient's PASI score. For assessing area and severity, the body is divided into four regions: head (10%); trunk (30%); upper extremities (20%); and lower extremities (40%). Each quadrant also was scored for the severity of erythema (E), infiltration (I) and desquamation (D), using a four point scale, in which 0=no symptoms present; 1=slight symptoms; 2=moderate symptoms; 3=striking symptoms; 4=exceptionally striking symptoms. Using a 6-point scale, each region was scored also for the percent of total area that was involved in the psoriatic manifestations of the disease, wherein 0=no involvement; 1=<10% involvement; 2=10-<30% involvement; 3=30-<50% involvement; 4=50-<70% involvement; 5=70-<90% involvement; 6=90-100% involvement. PASI scores were calculated according to the formula given below, in which E=severity score for erythrema, I=severity score for infiltration, D=severity score for desquamation and A=total area involved. In this formula, the letters "h," "t," "u" and "1" represent, respectively, the scores in each of the four body regions, i.e., head, trunk, upper extremities and lower extremities. The PASI score varies in steps of 0.1 units from 0.0 (no psoriatic lesions at all) to 72.0 (complete erythroderma of the severest possible degree).

$$PASI=0.1(Eh+Ih+Dh)Ah+0.3(Et+It+Dt)At+0.2(Eu+Iu+Du)Au+0.4(El+Il+Dl)Al$$

A secondary endpoint used for the psoriatic aspect of psoriatic arthritis was the Target Lesion Assessment Score. This score was determined for a single target lesion that was selected to be monitored throughout the trial. This measurement is a composite of four different evaluations: 1) plaque evaluation; 2) scaling; 3) erythrema; and 4) target lesion response to treatment. The following scale was used for the plaque elevation: 0=none (no evidence of plaque above normal skin level); 1=mild (slight but definite elevation above normal skin level); 2=moderate (moderate elevation with rounded or sloped edges to plaque); 3=severe (hard, marked elevation with sharp edges to plaque); 4=very severe (very marked elevation with very hard sharp edges to plaque). For the scaling assessment: 0=none (no scaling on the lesion); 1=mild (mainly fine scales, with some of the lesion at least partially covered); 2=moderate (somewhat coarser scales, most of the lesion at least partially covered); 3=severe (coarse, thick scales, virtually all the lesion covered, rough surface); 4=very severe (very coarse thick scales, all the lesions covered, very rough surface). For the erythema evaluation: 0=none (no erythema); 1=mild (light red coloration); 2=moderate (red coloration); 3=severe (very red coloration); 4=very severe (extreme red coloration). For target lesion response to treatment score: 0=completely cleared; 1=almost cleared (-90% improvement); 2=marked response (-75% improvement); 3=moderate response (-50% improvement); 4=slight response (-25% improvement); 5=condition unchanged; 6=condition worsened. The patient's Target Lesion Assessment Score was determined by summing the plaque, scaling, erythema and target lesion response scores for the monitored lesion. If the monitored lesion worsened, the percentage change from baseline was recorded as a negative number.

Treatment and placebo groups were compared in accord with the measurements described above, as well as for demo-

graphic and background characteristics; premature discontinuation rate; pain medication requirements; toxicities; serious adverse events; side effects reported by patients; number of weeks on drug until subjects met criteria for improvement, and response according to PsA subtype. Results were analyzed using standard statistical methods.

Dosing Regimen

Recombinant human TNFR:Fc (etanercept) from Immunex Corporation was used in this study. The gene fragments encoding the etanercept polypeptides were expressed in a Chinese hamster ovary (CHO) expression vector.

TNFR:Fc was supplied as a sterile lyophilized powder containing 10 mg or 25 mg TNFR:Fc; 40 mg mannitol, USP; 10 mg sucrose, NF; and 1.2 mg tromethamine (TRIS), USP per vial. Patients received either a dose of 25 mg of etanercept or a placebo. Vials of etanercept or identically-appearing placebo were reconstituted by aseptic injection of 1.0 mL Bacteriostatic Water for Injection, USP, (containing 0.9% benzyl alcohol), and was not filtered during preparation or prior to administration. If storage was required, the reconstituted solutions were stored at 2-8° C. (36-46° F.) in the original vial or in a plastic syringe for a period of no longer than 28 days. Dose was not changed during the study. Study drug was given twice weekly at approximately the same time of day.

Results

Study drug was well tolerated in all patients, and adverse events were consistent with this population and were equally distributed among both treatment groups. As illustrated in Tables 1-4, etanercept induced a significant improvement as compared with the placebo group in Psoriatic Arthritis Response (Table 1), ACR20 (Table 2), ACR50 (Table 3), PASI score, 50% improvement (Table 4), PASI score, 75% improvement (Table 5) and improvement in Target Lesion Assessment Score (Table 6). The fractions shown in Tables 1-5 represent numbers of patients. For example, the first entry in Table 1, which is "4/30," indicates that 4 of 30 patients in the placebo group scored as "improved" according to the Psoriatic Arthritis Response measurements. The tables include P-values for the differences between the two study groups, the groups being labeled as "PLACEBO" and "TNFR:Fc." All of the tables include data calculated after the first four weeks of the open label extension portion of the study ("EXTENSION"), during which all of the patients in both study groups received etanercept.

Table 1 shows the number of patients in each treatment group who scored as "improved" according to the Psoriatic Arthritis Response scoring system described above. By four weeks, there was a highly significant difference between etanercept and placebo groups. Moreover, after being switched to etanercept during the extension, those patients who had received placebo during the blinded portion of the study were seen to exhibit an improvement over baseline (Table 1, Placebo, EXTENSION). These results indicate that etanercept acts rapidly to alleviate many aspects of psoriatic arthritis.

TABLE 1

Psoriatic Arthritis Response

	Placebo	TNFR:Fc	P-value
4 weeks	4/30 (13%)	23/30 (77%)	0.000
8 weeks	7/30 (23%)	25/30 (83%)	0.000
12 weeks	6/30 (20%)	26/30 (87%)	0.000
EXTENSION	17/23 (74%)	21/25 (84%)	0.356

Tables 2 and 3, respectively, illustrate the study results for the ACR20 and ACR50 endpoints. For either measure, a significant difference between etanercept and placebo groups was observed at all three time points during the blinded portion of the study. Given the differences between test and placebo groups after only four weeks of treatment (P=0.000 for ACR20 and P=0.011 for ACR50), these data suggest that notable improvement in ACR scores occurred within the etanercept group very soon after treatment was initiated, possibly after a single dose of etanercept. During the 4 week extension period, during which all of the patients received etanercept, a striking improvement in both ACR20 and ACR50 was seen in those patients who had received placebo during the first 12 weeks (Tables 2 and 3).

TABLE 2

ACR20 Response

	Placebo	TNFR:Fc	P-value
4 weeks	1/30 (3%)	18/30 (60%)	0.000
8 weeks	3/30 (10%)	19/30 (63%)	0.000
12 weeks	4/30 (13%)	22/30 (73%)	0.000
EXTENSION	11/23 (48%)	18/25 (72%)	0.093

TABLE 3

ACR50 Response

	Placebo	TNFR:Fc	P-value
4 weeks	0/30 (0%)	6/30 (20%)	0.011
8 weeks	1/30 (3%)	11/30 (37%)	0.001
12 weeks	1/30 (3%)	15/30 (50%)	0.000
EXTENSION	7/23 (30%)	11/25 (44%)	0.316

The results of the psoriasis evaluations are presented in Tables 4-6. Tables 4 and 5, respectively, present the numbers and percentages of patients in each group who exhibited a 50% or 75% improvement in PASI score, while Table 6 presents Target Lesion Assessment scores, these latter being denoted as percent improvement over baseline. The data in Tables 4-6 clearly indicate that etanercept induced an improvement in psoriasis for a large percentage of the patients who received it. When single lesions were evaluated (Table 6), the improvement in psoriasis was even more apparent than when PASI scores were used (Tables 4 and 5). It is notable also that, for either PASI scores (Tables 4 and 5) or Psoriasis Target Lesion Assessment Score (Table 6), the scores of the placebo group improved after these patients were switched to etanercept during the extension.

Though not shown in Table 6, Target Lesion Assessment Scores for patients who were concurrently receiving methotrexate (14 of the 30 patients in the etanercept group, and 14 patients in the placebo group) were compared with the scores of those patients who did not take methotrexate. Little difference in this index was noted between the patients who received methotrexate and those who did not receive it.

TABLE 4

PASI Score-50% Improvement

	Placebo	TNFR:Fc	P-value
4 weeks	0/19 (0%)	4/19 (21%)	0.037
8 weeks	1/19 (5%)	7/19 (37%)	0.019
12 weeks	4/19 (21%)	8/19 (42%)	0.165
EXTENSION	6/16 (38%)	6/15 (40%)	0.856

TABLE 5

PASI Response Rate 75% Improvement

	Placebo	TNFR:Fc	P-value
4 weeks	0/19 (0%)	1/19 (5%)	0.264
8 weeks	0/19 (0%)	2/19 (11%)	0.153
12 weeks	0/19 (0%)	4/19 (21%)	0.037
EXTENSION	1/16 (6%)	4/15 (27%)	0.113

TABLE 6

Psoriasis Target Lesion Assessment
(Percent Improvement or Worsening Compared with Baseline)

		Placebo	TNFR:Fc	P-value
4 weeks	Mean (SD)	2.7 (27.6)	21.2 (35.2)	0.120
	Median	0.0	14.3	
	MIN-MAX	−50.0 −50.0	−33.3 −100.0	
	N	19	19	
8 weeks	Mean (SD)	−7.5 (25.3)	28.5 (34.1)	0.003
	Median	0.0	29.2	
	MIN-MAX	−50.0 −20.0	−33.3 −100.0	
	N	17	18	
12 weeks	Mean (SD)	9.5 (23.2)	45.7 (31.6)	0.001
	Median	0.0	50.0	
	MIN-MAX	−25.0 −50.0	−16.7 −100.0	
	N	16	19	
EXTENSION	Mean (SD)	28.9 (41.2)	47.1 (35.8)	0.263
	Median	36.7	50.0	
	MIN-MAX	−100.0 −66.7	−33.3 −100.0	
	N	16	15	

What is claimed is:

1. A method of treatment comprising administering a dose of TNFR:Fc to a patient having psoriatic arthritis and/or plaque psoriasis,

wherein the dose is administered one time or two times per week, and

wherein the dose administered is 25-50 mg or 50-100 mg, and

wherein the dose is administered by subcutaneous injection.

2. The method of claim **1**, wherein the dose is administered once per week and is 50-100 mg.

3. The method of claim **1**, wherein the dose is administered twice per week.

4. The method of claim **3**, wherein the dose administered is 25-50 mg.

5. The method of claim **3**, wherein the dose administered is 50-100 mg.

6. The method of claim **1**, wherein the patient has plaque psoriasis.

7. The method of claim **1**, wherein the patient has psoriatic arthritis.

8. A method for treating plaque psoriasis comprising administering TNFR:Fc by subcutaneous injection to a patient having plaque psoriasis once or twice a week at a dose of 25-50 mg or a dose of 50-100 mg.

9. The method of claim **8**, comprising administering the TNFR:Fc once a week at a dose of 50-100 mg.

10. The method of claim **9**, comprising administering the TNFR:Fc once a week at a dose of 50 mg.

11. The method of claim **8**, comprising administering the TNFR:Fc twice a week at a dose of 50-100 mg.

12. The method of claim **11**, comprising administering the TNFR:Fc twice a week at a dose of 50 mg.

13. The method of claim **8**, comprising administering the TNFR:Fc twice a week at a dose of 25-50 mg.

14. The method of claim **13**, comprising administering the TNFR:Fc twice a week at a dose of about 25 mg.

15. The method of claim **8**, comprising administering the TNFR:Fc twice a week at a dose of 50-100 mg for at least 3 weeks and then administering the TNFR:Fc once a week at a dose of 50-100 mg or twice a week at a dose of 25-50 mg.

16. The method of claim **8**, wherein a steroid, vitamin D3 or an analog thereof, cyclosporine, a retinoid, acitretin, ultraviolet light B phototherapy, psoralen plus ultraviolet A (PUVA) phototherapy, fumaric acid, or methotrexate is administered concurrently with the TNFR:Fc.

17. A method for treating psoriatic arthritis comprising administering TNFR:Fc by subcutaneous injection to a patient having psoriatic arthritis, wherein the TNFR:Fc is administered once a week at a dose of 50-100 mg or wherein the TNFR:Fc is administered twice a week at a dose of 25-50 mg.

18. The method of claim **17**, wherein the TNFR:Fc is administered once a week at a dose of 50-100 mg.

19. The method of claim **18**, wherein the TNFR:Fc is administered once a week at a dose of 50 mg.

20. The method of claim **17**, wherein the TNFR:Fc is administered twice a week at a dose of 25-50 mg.

21. The method of claim **20**, wherein the TNFR:Fc is administered twice a week at a dose of 25 mg.

22. The method of claim **17**, wherein methotrexate, cyclosporine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID) is administered concurrently with the TNFR:Fc.

* * * * *

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June 14, 2013

VIA FEDERAL EXPRESS

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Re: U.S. Patents 8,063,182 and 8,163,522

Dear Gentlemen:

Our client, Sandoz Inc., has developed an etanercept product, biosimilar to Enbrel®, which they intend to market in the United States following necessary regulatory approvals. Sandoz's etanercept product is in late-stage development as you will have seen from the recent publication regarding intended Phase III clinical trials, and we expect appropriate FDA submissions to be made in 2014. Because Sandoz has expended significant investments in developing and validating this product, it is of critical and immediate importance for Sandoz to obtain intellectual property certainty in advance of its forthcoming FDA filing and expected commercialization.

In this respect, we understand that Hoffmann-La Roche, Inc. is the assignee and Amgen, Inc. is the exclusive licensee of two recently issued patents, U.S. Patent Nos. 8,063,182 and 8,163,522. Based on its public statements, we understand that Amgen contends that the '182 patent "describes and claims the fusion protein that is etanercept," and does not expire until November 2028. We understand that you contend the '522 patent claims certain methods of producing etanercept.

Sandoz contests the validity and infringement of these patents, which issued more than a decade after the original patents covering etanercept. We are writing to formally request a covenant not

to sue on the '182 and '522 patents. We want the covenant not to sue to extend to all successors, assigns, licensees, distributors, suppliers, manufacturers, affiliates and customers of Sandoz. Because these patents are invalid, we consider these terms to be non-negotiable. Please advise us if you are willing to grant this requested covenant not to sue.

Very truly yours,

James F. Hurst

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