
Subject:	Tumor Necrosis Factor Antagonists	Current Effective Date:	02/26/2009
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Description/Scope

This document addresses the indications for a class of drugs known as tumor necrosis factor (TNF) antagonists.

Infliximab (Remicade®, Centocor Inc., Malvern, PA), etanercept (Enbrel®, Immunex Corporation, Thousand Oaks, CA), adalimumab (Humira®, Abbott Laboratories, North Chicago, IL), and certolizumab pegol (Cimzia®, UCB, Inc., Smyrna, GA) are designed to neutralize inflammatory cytokines. Each drug has been approved by the U.S. Food and Drug Administration (FDA) for use in specific indications based on the available peer-reviewed evidence.

Note: Please refer to the following document for additional medical criteria for TNF antagonists for psoriasis and psoriatic arthritis:

- CG-DRUG-12 Biologics for Psoriasis and Psoriatic Arthritis

Position Statement

I. Infliximab (Remicade)

A. **Infliximab** is considered **medically necessary** for individuals who meet the following criteria:

1. Rheumatoid Arthritis (RA): In combination with methotrexate (or if the individual is intolerant to methotrexate, in combination with another immunosuppressive agent that has also been demonstrated to prevent the development of human anti-chimeric antibodies [HACA], i.e. azathioprine, cyclosporine or sulfasalazine), for reducing signs and symptoms and inhibiting the progression of structural damage and improving physical function in individuals 18 years and older with moderately to severely active RA who have had an inadequate response to one or more DMARDs (disease-modifying antirheumatic drugs such as methotrexate, sulfasalazine, hydroxychloroquine).
2. Crohn's Disease (CD): Indicated for individuals 18 years and older and pediatric patients (six years of age and older) for reducing signs and symptoms and inducing and maintaining clinical remission in individuals with moderately to severely active CD, and who have had an inadequate response or are unable to tolerate conventional therapies [e.g., sulfasalazine, mesalamine products, systemic corticosteroids, immunosuppressants (6-mercaptopurine, azathioprine, cyclosporine, or methotrexate)].

Indicated for the reduction in the number of draining enterocutaneous and rectovaginal fistulas in individuals with fistulizing CD of at least 3 months duration.

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Maintenance infusion therapy treatment in individuals 18 years and older and pediatric patients (six years of age and older) with fistulizing or moderately to severely active CD who have responded to previous therapy with infliximab.

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3. Ulcerative Colitis (UC): Indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in individuals 18 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapies [e.g. sulfasalazine or olsalazine, mesalamine products, systemic corticosteroids, or immunosuppressants (6-mercaptopurine, azathioprine, cyclosporine, or methotrexate)].
4. Ankylosing Spondylitis (AS): Indicated for reducing signs and symptoms of active AS in individuals 18 years and older when conventional therapies [e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, methotrexate] have failed or are not indicated.
5. Psoriatic Arthritis (PsA): Indicated for reducing signs and symptoms of active PsA, inhibiting the progression of structural damage, and improving physical function in individuals 18 years and older when conventional treatment options, including DMARD therapy, have failed to achieve an adequate clinical response or are medically contraindicated. Examples of DMARD therapy include methotrexate or sulfasalazine. Additional medical criteria for this use may apply (See CG-DRUG-12 Biologics for Psoriasis and Psoriatic Arthritis).
6. Chronic Moderate to Severe Plaque Psoriasis (Ps): Indicated for the treatment of individuals 18 years and older whose disease is not controlled with topical therapy; **and** phototherapy or other systemic therapies failed to achieve an adequate clinical response, or there is a medical contraindication to the use of phototherapy or other systemic therapies, for example, methotrexate. Additional medical criteria for this use may apply (See CG-DRUG-12 Biologics for Psoriasis and Psoriatic Arthritis).

B. Infliximab is considered **not medically necessary** for individuals with **any** of the following:

1. Currently receiving other TNF antagonists or anakinra (Kineret®);
2. Tuberculosis or other active serious infections or a history of recurrent infections;
3. Individuals who have not had a tuberculin skin test (TST) or Centers for Disease Control (CDC)-recommended equivalent to rule out latent tuberculosis;
4. Hypersensitivity to any murine proteins or other inactive components of infliximab;
5. Moderate to severe congestive heart failure (CHF)-New York Heart Association (NYHA) Class III/IV;
6. Multiple sclerosis or other demyelinating neurological disease;
7. Children with Crohn's disease less than six years of age;
8. Concurrent administration of live vaccines with infliximab (Remicade).

C. Infliximab is considered **investigational and not medically necessary** for all other indications, including, but not limited to treatment of asthma, Behcet's syndrome, chronic obstructive pulmonary disease, disc-herniation-induced sciatica, hairy cell leukemia, graft-versus-host disease (GVHD), hidradenitis suppurativa, juvenile idiopathic arthritis, sarcoidosis, Still's Disease, Sjögren's syndrome, Takayasu arteritis, uveitis, and Wegener's granulomatosis.

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II. Etanercept (Enbrel)

A. **Etanercept** is considered **medically necessary** for individuals who meet the following criteria:

1. Rheumatoid Arthritis: In combination with methotrexate or alone, is indicated for reducing signs and symptoms, inducing major clinical response, and inhibiting the progression of structural damage and improving physical function in individuals 18 years and older with moderately to severely active RA who have had an inadequate response to one or more DMARDs.
2. Juvenile Idiopathic Arthritis (JIA): In combination with glucocorticoids, NSAIDs, analgesics or alone, is indicated for pediatric patients ages 2 and older with moderately to severely active polyarticular-course JIA (previously known as juvenile rheumatoid arthritis or JRA) who have had an inadequate response to one or more DMARDs.
3. Chronic Moderate to Severe Plaque Psoriasis: In individuals 18 years and older whose disease is not controlled with topical therapy; **and** phototherapy or other systemic therapies failed to achieve an adequate clinical response, or there is a medical contraindication to the use of phototherapy or other systemic therapies, for example, methotrexate. Additional medical criteria for this use may apply (See CG-DRUG-12 Biologics for Psoriasis and Psoriatic Arthritis).
4. Psoriatic Arthritis: Indicated for reducing signs and symptoms of active PsA, inhibiting the progression of structural damage, and improving physical function in individuals 18 years and older when conventional treatment options, including DMARD therapy, have failed to achieve an adequate clinical response or are medically contraindicated. Examples of DMARD therapy include methotrexate or sulfasalazine. Additional medical criteria for this use may apply (See CG-DRUG-12 Biologics for Psoriasis and Psoriatic Arthritis).
5. Ankylosing Spondylitis: Indicated for reducing signs and symptoms of active AS in individuals 18 years and older when conventional therapies (e.g., NSAIDs, sulfasalazine, methotrexate) have failed or are not indicated.

B. **Etanercept** is considered **not medically necessary** for individuals with **any** of the following:

1. Currently receiving cyclophosphamide therapy, other TNF antagonists, or anakinra (Kineret);
2. Tuberculosis or other active serious infections, or a history of recurrent infections;
3. Individuals who have not had a TST or a CDC-recommended equivalent to rule out latent tuberculosis;
4. Latex allergy as etanercept (Enbrel) prefilled syringe cover contains latex;
5. Multiple sclerosis or other demyelinating neurological disease;
6. Moderate to severe CHF - NYHA Class III/IV;
7. Concurrent administration of live vaccines with etanercept (Enbrel).

C. **Etanercept** is considered **investigational and not medically necessary** for all other indications, including, but not limited to treatment of asthma, disc-herniation-induced sciatica, graft-versus-host disease (GVHD), inclusion-body myositis, inflammatory bowel disease, hidradenitis suppurativa, sarcoidosis, septic shock, Sjögren's syndrome, and Wegener's granulomatosis.

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III. Adalimumab (Humira)

A. **Adalimumab** is considered **medically necessary** for individuals who meet the following criteria:

1. Rheumatoid Arthritis: In combination with methotrexate, other DMARDs or alone is indicated for reducing signs and symptoms, inducing major clinical response, and inhibiting the progression of structural damage and improving physical function in individuals 18 years and older with moderately to severely active RA who have had an inadequate response to one or more DMARDs.
2. Juvenile Idiopathic Arthritis (JIA): Indicated for reducing signs and symptoms of moderately to severely active polyarticular JIA in pediatric patients 4 years of age and older. Adalimumab can be used alone or in combination with methotrexate.
3. Psoriatic Arthritis: In combination with methotrexate, other DMARDs or alone is indicated for reducing signs and symptoms of active PsA, inhibiting the progression of structural damage and improving physical function in individuals 18 years and older when conventional treatment options, including DMARD therapy, have failed to achieve an adequate clinical response or are medically contraindicated. Examples of DMARD therapy include methotrexate or sulfasalazine. Additional medical criteria for this use may apply (See CG-DRUG-12 Biologics for Psoriasis and Psoriatic Arthritis).
4. Chronic Moderate to Severe Plaque Psoriasis. Indicated for the treatment of individuals 18 years and older whose disease is not controlled with topical therapy; **and** phototherapy or other systemic therapies failed to achieve an adequate clinical response, or there is a medical contraindication to the use of phototherapy or other systemic therapies, for example, methotrexate. Additional medical criteria for this use may apply (See CG-DRUG-12 Biologics for Psoriasis and Psoriatic Arthritis).
5. Ankylosing Spondylitis: Indicated for reducing signs and symptoms in individuals 18 years and older with active AS when conventional therapies (e.g., NSAIDs, sulfasalazine, methotrexate) have failed or are not indicated.
6. Crohn's Disease: Indicated for reducing the signs and symptoms of the disease and to induce and maintain clinical remission in individuals 18 years and older with moderately to severely active CD who:
 - a) have had an inadequate response or are unable to tolerate conventional therapies [e.g., sulfasalazine, mesalamine products, corticosteroids, immunosuppressants (6-mercaptopurine, azathioprine, cyclosporine, or methotrexate)], and have not been previously treated with a TNF antagonist; **or**
 - b) have had an inadequate response to conventional therapies [e.g., sulfasalazine, mesalamine products, corticosteroids, immunosuppressants (6-mercaptopurine, azathioprine, cyclosporine, or methotrexate)], and have previously been treated with infliximab, but have lost response to or are intolerant of infliximab.

B. **Adalimumab** is considered **not medically necessary** for individuals with **any** of the following:

1. Currently receiving other TNF antagonists or anakinra (Kineret)
2. Tuberculosis or other active serious infections, including chronic or localized infections;
3. Individuals who have not had a TST or CDC-recommended equivalent to rule out latent tuberculosis;
4. Latex allergy as adalimumab (Humira) prefilled syringe cover contains latex;
5. Multiple sclerosis or other demyelinating neurological disease;

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6. Concurrent administration of live vaccines with adalimumab (Humira);
7. New onset or worsening CHF.

C. **Adalimumab** is considered **investigational and not medically necessary** for all other indications.

IV. **Certolizumab pegol (Cimzia)**

A. **Certolizumab pegol** is considered **medically necessary** for individuals 18 years and older who meet the following criteria:

1. Crohn’s Disease: Indicated for reducing signs and symptoms of CD and maintaining clinical response in individuals with moderately to severely active disease who have had an inadequate response or are unable to tolerate conventional therapies [e.g., sulfasalazine, mesalamine products, corticosteroids, immunosuppressants (6-mercaptopurine, azathioprine, cyclosporine, or methotrexate)].

B. **Certolizumab pegol** is considered **not medically necessary** for individuals with **any** of the following:

1. Currently receiving other TNF antagonists or anakinra (Kineret);
2. Tuberculosis or other active serious infections, including chronic or localized infections;
3. Individuals who have not had a TST or CDC-recommended equivalent to rule out latent tuberculosis;
4. Multiple sclerosis or other demyelinating neurological disease;
5. Individuals with CHF who develop new symptoms or worsening symptoms of pre-existing CHF;
6. Concurrent administration of live (including attenuated) vaccines with certolizumab pegol (Cimzia).

C. **Certolizumab pegol** is considered **investigational and not medically necessary** for all other indications.

Dosing Information

Agent	Dosage Forms	Dosing
Cimzia	200 mg vials for reconstitution	<ul style="list-style-type: none"> • Adult Crohn’s Disease: 400 mg, given as two subcutaneous (SC) injections of 200 mg initially, and at weeks 2 and 4. If response occurs, follow with 400 mg SC every four weeks. Current Product Information (PI) requires administration by a healthcare professional.
Enbrel	25 mg and 50 mg single use prefilled syringe or a single-use prefilled SureClick™ autoinjector; 50 mg dose can be given as two 25 mg	<ul style="list-style-type: none"> • Adult Rheumatoid Arthritis: 50 mg SC weekly given as one 50 mg injection on one day A 50 mg dose can be given as two 25 mg SC injections in one day or 3 or 4 days apart. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics may be continued during treatment. • Juvenile Idiopathic Arthritis (ages 2 to 17 years): 0.8 mg/kg/wk up to a maximum of 50 mg SC/week given as one or two injections in one day or separated by 72 to 96 hours. The 25 mg prefilled syringe is not recommended for pediatric patients weighing less than 31 kg (68 lbs). Patients weighing 63kg (138 lbs or more) can use the 50mg prefilled syringe or SureClick™ autoinjector as a single dose. • Adult Ankylosing Spondylitis: 50 mg SC weekly given as one 50 mg injection

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Agent	Dosage Forms	Dosing
	<p>SC injections using prefilled syringes or multiple-use vials.</p>	<p>on one day. A 50 mg dose can be given as two 25 mg SC injections in one day or 3 or 4 days apart. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics may be continued during treatment.</p> <ul style="list-style-type: none"> • Adult Psoriatic Arthritis: 50 mg SC weekly given as one 50 mg injection on one day. A 50 mg dose can be given as two 25 mg SC injections in one day or 3 or 4 days apart. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics may be continued during treatment. • Adult Plaque Psoriasis: 50 mg SC twice weekly given 3 or 4 days apart for 3 months followed by a reduction to the maintenance dose of 50 mg SC weekly. Starting doses of 25 mg or 50 mg per week were also shown to be efficacious in the clinical studies (Enbrel Product Information, 2008).
Humira	<p>20 mg prefilled syringe: 40 mg single use prefilled glass syringe or pen</p>	<ul style="list-style-type: none"> • Adult Rheumatoid Arthritis: 40 mg SC every other week. In some individuals not on methotrexate additional benefit may be derived from increasing the dosing frequency to 40 mg SC once weekly. • Adult Psoriatic Arthritis: 40 mg (0.8 mL) SC every other week. • Adult Plaque Psoriasis: 80 mg SC initial dose, followed by 40 mg (0.8 mL) SC every other week starting one week after initial dose. • Adult Ankylosing Spondylitis: 40 mg SC every other week. • Adult Crohn's Disease: an induction dose of 160 mg with an 80 mg dose at week two, followed by maintenance dose of 40 mg every other week beginning at week four. The initial dose may be given as four injections on one day, or divided over two days. • Juvenile Idiopathic Arthritis: Pediatric patients (4 to 17 years of age). Patients weighing 15 kg (33 lbs) to <30 kg (66 lbs) 20 mg every other week (Can use 20 mg pre-filled syringe). Patients weighing ≥30 kg (66 lbs) 40 mg every other week (Can use pen or 40 mg pre-filled syringe).
Remicade	<p>100 mg single use vial</p>	<ul style="list-style-type: none"> • Adult Rheumatoid Arthritis: 3mg/kg IV in combination with methotrexate at 0, 2, and 6 weeks then every 8 weeks thereafter. For patients with an incomplete response, the dose may be increased up to 10mg/kg every 4 weeks. Risk of serious infection is increased with higher doses. Remicade may be used in combination with methotrexate or if the patient is intolerant to methotrexate, in combination with another immunosuppressive drug. • Adult Ankylosing Spondylitis: 5 mg/kg IV at 0, 2, and 6 weeks then every 6 weeks thereafter. • Adult Psoriatic Arthritis: 5 mg/kg IV at 0, 2, and 6 weeks then every 6** to 8 weeks thereafter (AAD, 2008). ** Please note that for this condition, the administration of Remicade at every 6 weeks is more frequent than the FDA label indication of every 8 weeks. • Crohn's Disease or Fistulizing Crohn's Disease: In pediatric patients (6 years of age and older) and individuals 18 years of age and older, 5 mg/kg IV at 0, 2, and 6 weeks then every 8 weeks thereafter. If the individual responds and then

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Agent	Dosage Forms	Dosing
		<p>loses response, consideration may be given to increase to 10 mg/kg IV or increase the frequency of administration from every 8 weeks thereafter to every 6 weeks thereafter**. Patients who do not respond by week 14 are unlikely to respond and should be considered for discontinuation of therapy.</p> <p><i>**Please note that for these conditions, the dose escalation of Remicade for pediatric patients to 10 mg/kg IV and the frequency of administration at every 6 weeks for adults and pediatric patients are more frequent than the FDA label indication of every 8 weeks.</i></p> <ul style="list-style-type: none"> • Adult Ulcerative Colitis: 5 mg/kg IV at week 0, 2, and 6 weeks then every 8 weeks thereafter. • Adult Plaque Psoriasis: 5 mg/kg IV at week 0, 2, and 6 weeks then every 6** to 8 weeks thereafter (AAD, 2008). <p><i>** Please note that for this condition, the administration of Remicade at every 6 weeks is more frequent than the FDA label indication of every 8 weeks.</i></p>

Note: There is currently no evidence available in the peer reviewed literature to support the use of one of these TNF products (adalimumab [Humira], etanercept [Enbrel], or infliximab [Remicade]) over the other for the specific indications of rheumatoid arthritis or psoriatic arthritis.

Combination therapy: Current evidence indicates in adult patients with RA, use of methotrexate plus a TNF antagonist as combination therapy, is more efficacious than monotherapy with any of the TNFs. Remicade is only approved by the FDA in adult RA as combination therapy with methotrexate.

Rationale

Remicade (infliximab), Enbrel (etanercept) Humira (adalimumab) and Cimzia (certolizumab pegol) belong to a class of drugs known as tumor necrosis factor (TNF or TNF-α) antagonists, which are designed to neutralize inflammatory cytokines. Each has been approved by the FDA for use in specific indications based on the available peer-reviewed evidence.

Infliximab (Remicade)

The patient selection criteria outlined above were derived from the FDA-approved prescribing information for Remicade, the studies presented to the FDA in support of the pre-market approval application, and studies in the peer-reviewed published medical literature. Remicade is FDA approved for adult rheumatoid arthritis, adult and pediatric Crohn’s disease (CD), ulcerative colitis, adult active ankylosing spondylitis, adult active psoriatic arthritis and adult plaque psoriasis.

The majority of children and adolescents with refractory CD appear to respond to infliximab therapy, whether the drug is used to treat inflammatory or fistulizing disease. The limiting factors appear similar to the adult experience: lack of a maintained response, potential allergic reaction, and the fact that long-term side effects (if any) from this drug have not yet been established. Recently, the FDA mandated that the safety and effectiveness of infliximab and

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other TNF- α agents be monitored in children and adolescents (CCFA, 2009; FDA, June 2008). Hyams and colleagues (2007) performed the first pediatric trial (REACH trial) aimed at evaluating the efficacy of infliximab as maintenance therapy in children ($n=112$) with moderate to severe CD. In this multicenter, randomized, open-label cohort study, the use of infliximab as scheduled maintenance therapy was compared to two different schedules: repeat infliximab infusions of 5 mg/kg at 2- versus 3-month intervals. At the endpoint visit of 54 weeks, 29 of 52 patients (56%) of the 2-month (8 weeks) interval group were in clinical remission compared to 12 of 51 children (23.5%) in the 3-month (12 weeks) interval group. The results of this study were the basis for the FDA approval of infliximab for pediatric CD. In the crossover arm of this study, patients who lost clinical response to infliximab were eligible to receive treatment more frequently, at higher doses, or both. Of the 32/35 evaluable patients who crossed over to the higher dose of 10 mg/kg every 8 weeks, 24 (75%) regained response after crossing over, including 5/9 (55.6%) who initially received infliximab 5 mg/kg every 8 weeks and subsequently crossed over to infliximab 10 mg/kg every 8 weeks, and 19/23 patients (82.6%) who initially received infliximab 5 mg/kg every 12 weeks and subsequently crossed over to receive either infliximab 10 mg/kg (12/13, 92.3%) or 5 mg/kg (7/10, 70.0%) every 8 weeks. However, the small patient population in the crossover arm of the study was not sufficiently powered to allow FDA approval of dose escalation for pediatric CD patients who initially responded but lose clinical response to infliximab (Hyams, 2007).

A subsequent prospective, multicenter, inception cohort study assessed the long-term outcome of infliximab maintenance therapy in a subgroup of children with CD enrolled in the Pediatric Inflammatory Bowel Disease Registry (Hyams, 2008). Children eligible to participate were under the age of 16 and newly diagnosed with IBD at a pediatric gastroenterology center in the U.S. and Canada collectively ($n=21$). During the entire first, second, and third years of maintenance therapy, 64% (78/121), 70% (50/71), and 83% (30/36), respectively, achieved sustained clinical response; sustained remission was achieved in 26%, 44%, and 33%, respectively. These findings, however, should be considered in the context of the following limitations. This study was observational and not a formal clinical trial. Dose escalation or decreased dosing intervals at any time during follow-up were required in 63/128 (49%) of patients in the outcome cohort. Sixty-five percent of these patients had their dose increased from 5 mg/kg to 10 mg/kg and the remainder had their interval reduced from every 8 weeks to at least every 6 weeks. Fifteen of these 63 patients (24%) eventually required both a dose increase and interval decrease during follow-up. It was noted that the occurrence of adverse events was not related to dose escalation.

Given the aggressive nature of pediatric onset CD, individualized treatment takes numerous factors into account: the specific disease manifestations such as location of inflammation in the intestines, duration, and prior response to therapy, and the child's age and weight. Because the incidence of pediatric onset CD is increasing and recent reports confirm that the disease has a more aggressive presentation and poorer prognosis than adult onset CD (Van Limbergen, 2008), pediatric gastroenterologists recognize the importance of achieving a sustained remission in their patients to prevent rapid progression from uncomplicated to complicated CD. An additional benefit of the use of infliximab has been demonstrated on pediatric growth failure which affects 15-40% of children presenting with CD (Newby, 2005). Despite the suggestion that longitudinal observational studies beyond three years in larger sample populations of children with CD are necessary to determine the long-term safety of infliximab therapy (Hyams, 2008), pediatric gastroenterologists agree that the benefits of a sustained clinical response and remission outweigh the risks associated with the use of infliximab, and, that there does not appear to be an increase risk of adverse events associated with dose escalation. Therefore, if the pediatric CD patient responds and then loses response, consideration may be given to increase infliximab dosing to 10 mg/kg or increase the frequency of administration from every 8 weeks to every 6 weeks thereafter. This dose escalation of infliximab for pediatric CD

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patients from 5 mg/kg to 10 mg/kg, and the frequency of administration at every 6 weeks are more frequent than the current FDA label indication of every 8 weeks.

The American Hospital Formulary Service® (AHFS® 2009) notes that infliximab has been used in a limited number of patients with Behcet's syndrome, however, further study is needed to evaluate the safety and efficacy of the drug in this disease. The peer-reviewed literature consists of case series and case reports that suggest improvement in orogenital ulceration, skin lesions, ocular, and neurological symptoms with the use of infliximab in treatment-resistant Behcet's disease. In addition, infliximab has been used in combination with prednisone, methotrexate, or azathioprine in a number of small, open-label prospective and retrospective studies of patients with sight-threatening, relapsing uveitis in Behcet's disease, refractory to immunosuppressive regimens (Niccoli, 2007; Tognon, 2007; Tugal-Tutkun, 2005). In these studies, the investigators report a lack of serious adverse events and suggest that infliximab was effective in suppressing the occurrence of uveitis attacks during the treatment period, had a corticosteroid-sparing effect, and favorable implications for the visual prognosis of patients with resistant Behcet's uveitis. However, ocular and systemic manifestations tended to recur after infliximab withdrawal or when the interval between infliximab courses was longer than eight weeks (Tognon, 2007). In a prospective, open-label phase II clinical trial (n=23) to assess the effectiveness of infliximab in treating refractory autoimmune uveitis, Suhler and colleagues (2005) suggested that infliximab was an effective short-term immunosuppressive agent in most of the patients, with 18 of 23 meeting criteria for clinical success at week ten and in patients (7 of 14) able to complete 50 weeks of therapy. Although some patients achieved benefit, the rate of serious toxic effects was unexpectedly high. The investigators concluded that further long-term studies were warranted to determine the safety and efficacy of infliximab in treating intraocular inflammation. In summary, further trials are required in the form of randomized, double-blinded, controlled studies with long-term follow-up to evaluate the safety and efficacy of infliximab in patients with Behcet's syndrome and its complications, Behcet's-related uveitis, and autoimmune uveitis/intraocular inflammation.

Although infliximab has been used in patients with juvenile idiopathic arthritis (JIA), the safety and efficacy has not been established for this usage (AHFS, 2009). A multicenter, randomized, double-blind, placebo-controlled study (n=117), failed to establish the efficacy of infliximab in pediatric patients with JIA; the study yielded high placebo response rates and a higher rate of immunogenicity compared to that observed in adults patients. Although the study did not demonstrate a statistically significant difference between infliximab and placebo (p=0.12), it appears that this was in part due to the low dosing of infliximab (3 mg/kg) and the exclusion of 45 patients from the efficacy analysis. This high withdrawal rate, due to data collection irregularities at one investigator site, may have resulted in a loss of the ability to detect the difference in efficacy of infliximab between the groups (Ruperto, 2007; Remicade Product Information, 2008). Long-term safety concerns of infliximab, including development of malignancies, have not been determined in this population. Infliximab has been studied as an adjunct to second-line agents for the treatment of JIA-associated uveitis in small, retrospective case series and uncontrolled trials (Ardoin, 2007; Gallagher, 2007; Kahn, 2006; Saurenmann, 2007; Sharma, 2008; Sobrin, 2007; Tynjälä, 2007) and a cross-sectional multinational cohort survey (Foeldvari, 2007). Overall, the study investigators report that infliximab (higher doses in some patients) is an effective, well-tolerated therapeutic agent that resulted in a reduction in symptoms or control of ocular inflammation in patients with chronic, medically refractory, JIA-associated uveitis. In addition to infliximab-induced remission, some patients were able to reduce or discontinue corticosteroid and other immunosuppressant therapy. Some patients with active uveitis who had previously failed other treatments, responded to infliximab better than etanercept in controlling inflammation (Tynjälä, 2007) and improving visual acuity, glaucoma and complication rates (Saurenmann, 2007). Tynjälä and colleagues also reported findings during the two-year follow-up where "the frequency of long-term complications of uveitis seemed to increase despite

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decreased ocular inflammatory activity.” Studies of infliximab for pediatric JIA-related uveitis have been hampered by variables including small numbers, the uncontrolled, retrospective nature of most reports, differential follow-up times, lack of standardization of disease activity and disease outcome measures, reports on patients with a variety of underlying diagnoses, and the concomitant use of other drug therapies. In a recent prospective, comparative case series of children with JIA-related refractory uveitis, during the first year of treatment, 13 of 15 children achieved a complete remission on infliximab over a median period of 10 weeks (range 6-16 weeks) after starting therapy. No relapse of uveitis occurred in these 13 children during the first year, while before starting infliximab, the median number of relapses was four per year (range 2-6). However, all 13 responder children relapsed after the first year of infliximab infusions. At first relapse of uveitis, median follow-up on treatment was 15 months (range 12-23) and the median number of infusions was 12 (range 10-18). The investigators concluded that even if limited to a small cohort, their data showed that infliximab appeared to be an effective treatment for uveitis in the short term, “but its efficacy seems to wane over time” (Simonini, 2008). Kahn and colleagues (2007) concluded that larger, randomized, controlled studies may provide a better understanding of the dose, interval, and duration of treatment needed and data on long-term safety of the use of infliximab for JIA-associated uveitis. To date, no prospective, placebo-controlled data exists regarding the efficacy of infliximab for the treatment of JIA-associated uveitis (Foeldvari, 2007).

The use of infliximab has been studied as an adjunct to immunosuppressive therapy in a small case series (n=6) (Lamprecht, 2002) of patients with Wegener’s granulomatosis and in an open-label pilot study (n=10) (Bartolucci, 2002) of patients with active systemic vasculitides, including Wegener’s granulomatosis. Treatment led to remission in five of six patients in the case series and symptomatic improvement in the patients in the open-label pilot study. However, further randomized controlled trials of larger patient populations are needed to determine the efficacy and safety of infliximab for this condition.

Because of evidence that tumor necrosis factor may play a role in progression of heart failure, infliximab has been investigated for the management of chronic heart failure in patients with moderate to severe (NYHA class III to IV) CHF (AHFS, 2009). In a phase II, double-blind, placebo-controlled, pilot study, patients with stable NYHA class III or IV CHF (left ventricular ejection fraction $\leq 35\%$) were randomized to receive placebo (n=49), infliximab 5 mg/kg (n=50), or infliximab 10 mg/kg (n=51) at 0, 2, and 6 weeks after randomization and prospective follow-up for 28 weeks. Neither dose of infliximab improved clinical status at 14 weeks, the primary endpoint of the study, despite suppression of inflammatory markers (C-reactive protein and interleukin-6) and a modest increase in ejection fraction in the patients receiving 5 mg/kg (p=0.013). In addition, after 28 weeks, 13, 10, and 20 patients were hospitalized for any reason in the placebo, 5 mg/kg infliximab, and 10 mg/kg infliximab groups, respectively. The combined risk of death from any cause or hospitalization for heart failure through 28 weeks was increased in the patients randomized to 10 mg/kg infliximab (HR 2.84, 95% CI 1.01 to 7.97; nominal p=0.043). The investigators concluded that short-term use of infliximab did not improve and high doses (10 mg/kg) adversely affected the clinical condition of patients with moderate-to severe chronic heart failure (Chung, 2003).

Infliximab has been investigated as a treatment for conditions including asthma (Erin, 2006), chronic obstructive pulmonary disease (Rennard, 2007; van der Vaart, 2005), disc herniation-induced sciatica (Korhonen, 2006), graft-versus-host disease (GVHD) (Hamadani, 2008), hidradenitis suppurativa (Kaufman, 2005), juvenile idiopathic arthritis (Ruperto, 2007), orbital/ocular-related uveitis or scleritis (Prendiville, 2008), pyoderma gangrenosum, Still’s Disease, Sjogren’s syndrome (Mariette, 2004), Takayasu arteritis (Hoffman, 2004), and treatment-resistant, chronic sarcoidosis (Baughman, 2006; Rossman, 2006). The available peer-reviewed published literature for these conditions consists of case reports, uncontrolled case series, small, open-label prospective pilot studies and

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randomized controlled trials reporting short-term treatment outcomes. While some of these reports present a positive effect on the clinical manifestations of these diseases, there is a lack of larger scale, randomized controlled trials evaluating the long-term effects of infliximab compared to placebo (Suhler, 2005; Theodossiadis, 2007).

Etanercept (Enbrel)

Enbrel has been approved by the FDA for rheumatoid arthritis, psoriatic arthritis, chronic plaque psoriasis, ankylosing spondylitis, and polyarticular-course juvenile idiopathic arthritis.

Enbrel is currently being investigated for the management of Wegener's granulomatosis and is designated as an orphan drug by the FDA for this use (AHFS, 2009). In an open-label study in a limited number of patients with Wegener's granulomatosis who had not responded adequately to standard therapy (i.e., prednisone, cyclophosphamide, methotrexate, azathioprine, cyclosporine), addition of etanercept (25 mg subcutaneously twice weekly) for a mean of 21 weeks resulted in a positive clinical response in most patients, although limited flares and persistent minor features of active disease occurred frequently (Stone, 2001). However, in a randomized placebo controlled study of patients with Wegener's granulomatosis (n=180), the rates of sustained remission, sustained periods of low level disease activity, and time needed to achieve these measures in patients receiving etanercept in combination with standard therapy (glucocorticoids plus cyclophosphamide or methotrexate) were similar to those who received standard therapy alone. Additionally, disease flares did not differ significantly between the groups. In addition, solid malignant tumors developed in a significant group (p=0.01) of these etanercept-treated patients, (n=6 of 89) versus placebo group (n=0) (Wegener's Granulomatosis Etanercept Trial (WGET) Research Group, 2005; Stone, 2006).

Etanercept has been investigated for the treatment of heart failure (AHFS, 2009) in two clinical studies, the RECOVER and RENAISSANCE trials, both terminated early because of a lack of efficacy of the drug (Louis, 2001; Enbrel Product Information, 2008). In the RECOVER trial, patients with NYHA class III to IV chronic heart failure and a left ventricular ejection fraction ≤ 0.30 received placebo (n=373) or subcutaneous etanercept in doses of 25 mg every week (n=375) or 25 mg twice per week (n=375). In RENAISSANCE, patients received placebo (n=309), etanercept 25 mg twice per week (n=308), or etanercept 25 mg 3 times per week (n=308). The primary end point of each individual trial was clinical status at 24 weeks. Analysis of the effect of the two higher doses of etanercept on the combined outcome of death or hospitalization due to chronic heart failure from the two studies was also planned. In a subsequent publication, The Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL), Mann and colleagues (2004) reported that etanercept had no effect on clinical status in RENAISSANCE (p=0.17) or RECOVER (p=0.34) and had no effect on the death or chronic heart failure hospitalization end point (etanercept to placebo relative risk=1.1, 95% CI 0.91 to 1.33, p=0.33). Mann and colleagues concluded that the results of the RENEWAL report rule out a clinically relevant benefit of etanercept on the rate of death or hospitalization due to chronic heart failure.

A small (n=10), open-label, prospective, phase II study recently evaluated the safety and efficacy of etanercept for the treatment of hidradenitis suppurativa. Etanercept was administered subcutaneously in a dose of 50 mg once weekly for 12 weeks. Treatment outcomes were measured at 12 and 24 weeks with disease activity assessed by physicians who were unaware of the treatment protocol, and by the patients who performed a self-evaluation using the visual analogue scale (VAS). At week 12 and week 24, a >50% score improvement was reported in disease activity in six and seven patients, respectively, without adverse events. The VAS was decreased compared with baseline in seven patients at week 12 and six patients at week 24. The investigators suggested that despite these

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encouraging results, there is a need for a double-blinded, placebo-controlled trial to fully evaluate the safety and efficacy of etanercept for treatment of hidradenitis suppurativa (Giamarellos-Bourboulis, 2008).

Etanercept has been investigated as a treatment for asthma (mild to moderate disease; corticosteroid-refractory) (Berry, 2006; Morjaria, 2008); disc-herniation-induced sciatica (Cohen, 2007), graft-versus-host disease (steroid-refractory, acute/aGVHD and chronic/cGVHD), inclusion-body myositis (Barohn, 2006), septic shock (Fisher, 1996), and Sjögrens syndrome (Sankar, 2004; Zandbelt, 2004; Mavragani, 2007). While some of these studies report positive outcomes on the clinical manifestations of these diseases, there is a lack of large scale, randomized controlled trials evaluating the long-term effects of etanercept compared to placebo. Specifically, data reported by Busca and colleagues (2007) in a small trial (n=21) indicated that etanercept was well tolerated and induced a high response rate in patients with steroid-refractory aGVHD and cGVHD, particularly in the setting of GI involvement, following allogeneic hematopoietic stem cell transplant. These results are similar to those reported by Chiang and colleagues in an earlier study (2002), where etanercept was given without adverse side effects in an eight-week treatment course to ten patients with cGVHD post allogeneic hematopoietic stem cell transplant. The authors concluded, however, that these results were preliminary and warranted further investigation in larger, prospective trials.

Adalimumab (Humira)

Humira has been approved by the FDA for treatment of moderate to severe Crohn's disease, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis in adults, and juvenile idiopathic arthritis in patients four years of age and older. Humira can be used alone or in combination with methotrexate or other DMARDs in rheumatoid arthritis and alone or in combination with DMARDs in psoriatic arthritis. Humira can be used alone or in combination with methotrexate in pediatric patients with juvenile idiopathic arthritis.

Certolizumab pegol (Cimzia)

Cimzia has been approved by the FDA for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adults with moderately to severely active disease who have had an inadequate response to conventional therapy. The efficacy and safety of certolizumab pegol (Cimzia) was assessed in two, double-blind randomized, placebo-controlled trials in adults ages 18 and older with moderately to severely active CD as defined by a Crohn's Disease Activity Index (CDAI) of 220 to 450 points, inclusive. Certolizumab pegol was administered subcutaneously at a dose of 400 mg in both studies. Stable concomitant medications for CD were permitted. In the PRECISE I trial (Sandborn, 2007), 662 adults were stratified according to baseline levels of C-reactive protein (CRP) and were randomly assigned to receive either 400 mg of certolizumab pegol or placebo subcutaneously at weeks 0, 2, and 4 and then every 4 weeks. Primary end points were the induction of a response at week 6 and a response at both weeks 6 and 26. In the overall population, response rates at week 6 were 35% in the certolizumab group and 27% in the placebo group (p=0.02); at both weeks 6 and 26, the response rates were 23% and 16%, respectively (p=0.02). At weeks 6 and 26, the rates of remission in the two groups did not differ significantly (p=0.17). Serious adverse events were reported in 10% of patients in the certolizumab group and 7% of those in the placebo group; serious infections were reported in 2% and less than 1%, respectively. The investigators concluded that in adults with moderate-to-severe CD, induction and maintenance therapy with certolizumab pegol was associated with a modest improvement in response rates, as compared with placebo, but with no significant improvement in remission rates.

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In the PRECISE II trial (Schreiber, 2007), adults with moderate-to-severe CD received 400 mg of certolizumab pegol as induction therapy, administered subcutaneously at weeks 0, 2, and 4. Subjects with a clinical response (defined as reduction of at least 100 from the baseline score on the CDAI) at week 6 were stratified according to their baseline C-reactive protein level and were randomly assigned to receive 400 mg of certolizumab pegol or placebo every 4 weeks through week 24, with follow-up through week 26. Among subjects with a response to induction therapy at week 6 (428 of 668 or 64%), the response was maintained through week 26 in 62% of subjects with a baseline C-reactive protein level of at least 10 mg per liter (the primary end point) who were receiving certolizumab pegol (vs. 34% of those receiving placebo, $p < 0.001$) and in 63% of subjects in the intention-to-treat population who were receiving certolizumab pegol (vs. 36% receiving placebo, $p < 0.001$). Among subjects with a response to induction therapy at week 6, remission (defined by a CDAI score of ≤ 150) at week 26 was achieved in 48% of subjects in the certolizumab group and 29% of those in the placebo group ($p < 0.001$). Infectious serious adverse events (including one case of pulmonary tuberculosis) occurred in 3% of subjects receiving certolizumab pegol and in less than 1% of subjects receiving placebo. The investigators concluded that adults with moderate-to-severe CD, who had a response to induction therapy with 400 mg of certolizumab pegol, were more likely to have a maintained response and a remission at 26 weeks with continued certolizumab pegol treatment than with a switch to placebo.

Background/Overview**Pharmacology**

Tumor necrosis factor (TNF or TNF- α) is a member in a family of proteins which induce necrosis (death) of tumor cells and have a wide range of proinflammatory actions. They are a multifunctional cytokine or a small protein released by cells which has a specific effect on the interaction of the cell, on the communication between the cells or on the behavior of the cells. TNF antagonists (also known as TNF inhibitors) are drugs that target specific pathways of the immune system and either enhance or inhibit immune response. These substances, which are naturally produced in small quantities in the body, can now be produced in large quantities in the laboratory.

In 2006, Bongartz and colleagues described a meta-analysis assessing the increased risk of infection and malignancy in RA patients treated with infliximab and adalimumab. This meta-analysis confirmed the information included in the product labeling of these two agents regarding increased risk of malignancy and infection, with the increased risk of malignancy appearing to be dose dependant. This meta-analysis did not address any use of these agents for conditions other than RA. Additionally, no observations or assessments were made regarding these risks with any other biologic agents. All TNF antagonists carry precautions in their respective product labeling regarding the potential for an increased risk of lymphoma or malignancy. Information in the labeling states that causality has not been established to confirm that the risk is due to use of these agents or whether it is due to the underlying disease.

The TNF antagonists have also been associated with the potential worsening of CHF. Clinical trials evaluating Remicade and Enbrel showed an increase in worsening or new cases of CHF. Humira has not been studied in individuals with CHF, but case reports have shown an increased risk. All TNF antagonists carry precautions in their respective product labeling regarding this risk. Remicade at doses >5 mg/kg is contraindicated for use in individuals with moderate to severe heart failure.

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Treatment with TNF antagonists may also increase the risk of developing an autoimmune disorder such as a lupus-like syndrome. If symptoms develop suggestive of a lupus-like syndrome, the drug should be discontinued and the individual carefully monitored. All TNF antagonists carry precautions in their respective product labeling regarding this risk.

There are no adequate and well-controlled studies evaluating the use of the TNF antagonists in pregnant women. TNF antagonists should be used in pregnancy only if clearly needed; physicians are encouraged to monitor outcomes of pregnant women exposed to the TNF antagonists by enrolling them in a drug-specific pregnancy registry. Because of the potential for serious adverse reactions in nursing infants from the TNF antagonists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

On June 4, 2008, the FDA posted an *Early Communication About an Ongoing Safety Review of Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, and Cimzia)*. The FDA is investigating approximately 30 reports submitted to the Adverse Event Reporting System over a ten-year interval involving the possible association between the use of TNF antagonists (blockers) and the development of lymphoma and other cancers in children and young adults. These reports describe cancer occurring in these individuals who began taking TNF blockers (along with other immunosuppressive medicines such as methotrexate, azathioprine or 6-mercaptopurine) when they were 18 years of age or younger, to treat JIA, Crohn's disease or other diseases. Approximately half the cancers were lymphomas and included both Hodgkin's and non-Hodgkin's lymphoma, with other cancers reported as leukemia, melanoma, and solid organ tumors. The FDA reports "Long-term studies are necessary to provide definitive answers about whether TNF blockers increase the occurrence of cancers in children because cancers may take a long time to develop and may not be detected in short-term studies." The FDA has asked the makers of the TNF blockers approved for use in children (Remicade, Enbrel, and Humira) to provide information about all cases of cancer reported in children taking TNF blockers. The maker of Cimzia is required to conduct a study to assess long-term risks of the product, including lymphoma and other cancers. This study will begin in 2009 and take about 10 years to complete. In addition, the FDA has contacted medical experts to assess the potential association between TNF blockers and cancers, including lymphoma, and to determine if there are children and young adults with JIA and Crohn's disease who may be at particular risk for developing a lymphoma or other cancer. The prescribing information for all four TNF blockers includes a boxed warning to inform healthcare providers, parents, and caregivers about the possible risk of lymphoma and other cancers in children and young adults (FDA, June 2008).

On September 4, 2008, the FDA posted an alert notifying healthcare professionals that histoplasmosis and other invasive fungal infections are not consistently recognized in patients taking the TNF blockers. The delays in appropriate treatment have resulted in death in some patients who developed pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis and other opportunistic infections while taking TNF blockers. The FDA alert encourages patients taking TNF blockers to promptly seek medical attention when experiencing signs and symptoms of possible systemic fungal infection, such as fever, malaise, weight loss, sweats, cough, and/or dyspnea. Healthcare professionals were encouraged to ascertain if patients who present with these symptoms live in or have traveled to areas of endemic mycoses; consideration should be given to initiating empiric antifungal treatment until the pathogen(s) are identified if the patient presents with any of these symptoms (including pulmonary infiltrates or other serious systemic illness with or without concomitant shock) (FDA, September 2008).

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Infliximab (Remicade) is a chimeric (part mouse, part human) monoclonal antibody that blocks activity of a key biologic response mediator called “tumor necrosis factor (TNF) alpha.” The action of Remicade is to bind to and neutralize TNF-alpha on the cell membrane and in the blood supply and to destroy TNF-alpha producing cells, thus inhibiting inflammation. It also binds TNF-alpha in the intestines and reduces inflammation in Crohn's disease. Remicade is supplied as a sterile, white lyophilized powder in a 100 mg/2 mL vial for intravenous infusion. It is an infusible medication that has been approved for home IV therapy, hospital outpatient administration or physician office administration.

Possible Risks

Serious, even fatal, infections have been reported to occur during treatment with infliximab. Signs of infection such as fever or chills, sore throat, coughing, and congestion have been reported as well as redness, pain, or swelling of a skin wound or burning/difficult urination. Remicade carries a black box warning in the package labeling regarding the risk of tuberculosis (Tb), due to case reports of Tb (frequently disseminated or extrapulmonary at clinical presentation) in patients receiving Remicade. Patients should be evaluated for latent Tb infection with a tuberculin skin test (TST) or a CDC-recommended equivalent [e.g. QuantiFERON®-TB Gold test (QFT-G) (Cellestis Inc., North America, Valencia, CA)] prior to initiation of Remicade. All patients should be monitored during Remicade treatment for active Tb, even if the initial TST or CDC-recommended equivalent test is negative. Remicade recently received an additional black box warning indicating that rare post marketing cases of hepatosplenic T-cell lymphoma have been reported in adolescents and young adults with Crohn's disease treated with Remicade. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatosplenic T-cell lymphomas with Remicade have occurred in individuals on concomitant treatment with azathioprine or 6-mercaptopurine.

All pediatric Crohn's disease patients should be brought up-to-date with all vaccinations prior to initiating Remicade therapy. The interval between vaccination and initiation of Remicade therapy should be in accordance with current vaccination guidelines. Live vaccines should not be given concurrently while patients are receiving Remicade therapy. Remicade has not been studied in children with Crohn's disease less than six years of age. The long term (greater than one year) safety and effectiveness of Remicade in pediatric Crohn's disease patients have not been established in clinical trials.

Etanercept (Enbrel) is a dimeric fusion protein that binds specifically to TNF and blocks its interaction with cell surface TNF receptors. Enbrel is supplied as a 25 mg multi-use vial (requires reconstitution) and 25 and 50 mg/mL single-use prefilled syringes. A 50 mg dose can be given as two 25 mg SC injections using the 25 mg single-use prefilled syringes. When administered as two injections in adults or children, Enbrel should be given either on the same day or three or four days apart. It is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines it is appropriate and with medical follow-up, as necessary, after proper training in reconstitution and injection technique.

Possible Risks

In post-marketing reports, serious infections and sepsis, including fatalities, have been reported with the use of Enbrel. Many of these serious events have occurred in patients with underlying diseases that in addition to their rheumatoid arthritis could predispose them to infections. In March 2008, a black box warning was added to the prescribing information for Enbrel to further strengthen and clarify information regarding the risk of infections, including Tb in patients taking Enbrel; namely the new recommendation to screen for latent Tb infection with a

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TST or a CDC-recommended equivalent (e.g. QFT-G) prior to initiation of Enbrel. The revisions state that serious infections leading to hospitalization or death have been observed in patients treated with Enbrel, including bacterial sepsis and Tb. Patients should be educated about the symptoms of infection and closely monitored for signs and symptoms of infection during and after treatment with the drug. Patients who develop a new infection while undergoing treatment with Enbrel should be evaluated for appropriate antimicrobial treatment and, in patients who develop a serious infection, Enbrel should be discontinued.

Patients receiving Enbrel may receive concurrent vaccinations, except for live vaccinations. It is recommended that JIA patients, if possible, be brought up-to-date with all immunizations in accordance with current immunization guidelines prior to initiating Enbrel therapy. Patients with significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Adalimumab (Humira) is a recombinant human IgG1 monoclonal antibody specific for the human tumor necrosis factor and acts by blocking the interaction between TNF α and p55 and p75 receptors. It is supplied in a single-use, 1 mL prefilled glass syringe or pen containing 40 mg of Humira as a sterile, preservative-free solution for subcutaneous administration. Humira is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.

Possible Risks

Serious infections and sepsis, including fatalities, have been reported with the use of TNF antagonist or blocking agents, including Humira. Many of the serious infections have occurred in patients with concomitant immunosuppressive therapy, which in addition to their rheumatoid arthritis could predispose them to infection. Humira carries a black box warning in the package labeling regarding an increased risk of Tb, due to case reports of Tb (frequently disseminated or extrapulmonary at clinical presentation) in patients receiving Humira. Patients should be evaluated for latent Tb infection with a TST or a CDC-recommended equivalent (e.g. QFT-G) prior to initiation of Humira. Additionally, all patients should be monitored during Humira treatment for active Tb, even if the initial TST or CDC-recommended equivalent test is negative.

Individuals on Humira may receive concurrent vaccinations, except for live vaccines. It is recommended that JIA patients, if possible, be brought up-to-date with all immunizations in accordance with current immunization guidelines prior to initiating Humira therapy.

Certolizumab pegol (Cimzia) is a recombinant, humanized antibody Fab' fragment (PEGylated anti-TNF α), with specificity to human tumor necrosis factor alpha (TNF- α), a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol was shown in the clinical trials to selectively neutralize membrane-associated and soluble human TNF- α in a dose-dependent manner. It is supplied as a sterile, lyophilized powder for reconstitution, administered as a subcutaneous injection by a health care professional.

Possible Risks

Serious infections, sepsis, and cases of opportunistic infections, including fatalities, have been reported with the use of TNF blocking agents, including Cimzia. Many of the serious infections occurred in patients with concomitant immunosuppressive therapy, that in addition to their Crohn's disease, could predispose them to infections. The most common adverse reactions (incidence \geq 5% and higher than placebo) with Cimzia include upper respiratory

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tract infection, urinary tract infection, and arthralgia. Use of Cimzia may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating CIMZIA therapy. In the controlled studies of Cimzia for Crohn's disease and other investigational uses, there was one case of lymphoma among 2657 Cimzia-treated patients and one case of Hodgkin's lymphoma among 1319 placebo-treated patients. Cimzia carries a black box warning in the package labeling regarding the risk of Tb, invasive fungal, and other opportunistic infections, and some fatalities. Patients should be evaluated for latent Tb infection with a TST or CDC-recommended equivalent test (e.g. QFT-G) prior to initiation of Cimzia. In addition, all patients should be monitored during Cimzia treatment for active Tb, even if the initial TST or CDC-recommended equivalent is negative. In the clinical trials in patients with Crohn's disease, 4% of those receiving Cimzia developed new positive antinuclear antibodies (ANA) compared with 2% of those receiving placebo. A lupus-like syndrome has occurred in at least one patient. If a patient develops manifestations suggestive of a lupus-like syndrome, Cimzia should be discontinued. The safety and efficacy of Cimzia in patients with immunosuppression and in pediatric patients have not been established (AHFS, 2009).

Epidemiology***Ankylosing Spondylitis***

Ankylosing spondylitis is probably the most familiar spondyloarthropathy, which is characterized not by the inflammation of the synovium, as seen in rheumatoid arthritis, but inflammation of the enthesis, the site where ligaments, tendons, and joint capsules insert into bone. Inflammation around the vertebrae, face, joints and feet can lead to fibrosis, ossification, deformity, and ankylosis. Among whites the estimated prevalence rate of ankylosing spondylitis as defined by the (modified) New York criteria is about 197 per 100,000 in individuals in the United States with an age greater than 70 years. Ankylosing spondylitis is classified with the seronegative spondyloarthropathies as is Reiter's syndrome, reactive arthritis, and psoriatic arthritis. Conventional treatment for ankylosing spondylitis consists primarily of non-steroidal anti-inflammatory drugs (NSAIDs).

Crohn's Disease

Between 400,000 and 600,000 individuals in North America have Crohn's disease, and the natural history is marked by frequent exacerbations requiring treatment with corticosteroids, 5-aminosalicylate products and surgery. While an auto-reactive antibody has not yet been discovered, it is generally accepted that Crohn's disease is an autoimmune disease that occurs in genetically predisposed individuals; clinical presentation is primarily determined by the anatomic location of the disease. The most common presenting symptoms are fever, abdominal pain, and diarrhea with or without blood. Fistula formation, fissuring, discontinuous intestinal and transmural involvement with bowel-wall thickening and extracolonic manifestations such as arthritis, skin and eye manifestations, metabolic deficiencies, hypercoagulation, and hepatobiliary disease are frequent complications. The clinical course of Crohn's disease is chronic and intermittent and there is no known cure. Medical therapy includes the use of 5-aminosalicylic acid (5-ASA) preparations such as mesalamine, sulfasalazine, or olsalazine, glucocorticoids such as prednisone or budesonide, antibiotics, immunosuppressive drugs (6-MP/AZA), methotrexate and other anti-inflammatory agents.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a condition that describes arthritic inflammation of the synovium (lining of the joints) with an onset, typically before 16 years of age. Previously called juvenile rheumatoid arthritis, the name has been changed to reflect the difference between the juvenile (childhood) forms of arthritis and adult forms of

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arthritis. Although JIA is idiopathic (the cause is unknown), it is likely the result of a combination of genetic, infectious, and environmental factors. Because arthritis in children may resemble the joint pain associated with infections, cancer, bone disorders, and other inflammatory disorders, these potential causes should be excluded before the diagnosis of JIA can be made. JIA is categorized into five main types based on the number of joints involved during the first six months of disease and the involvement of other organs. These types include oligoarthritis, polyarthritis, systemic arthritis, enthesitis-related arthritis, and psoriatic arthritis. Treatment depends on the category of JIA and the extent of joint involvement. Medications are available to decrease the symptoms of joint pain and stiffness and alter the disease process, preventing permanent damage to the joint or joints (Ringold, 2005). Uveitis is the most common extra-articular manifestation of childhood JIA and can be acute anterior, recurrent anterior, chronic anterior, or anterior uveitis with vitritis. The chronic form of anterior uveitis, usually seen in JIA, is asymptomatic, typically occurs in females <4 years of age, and is strongly associated with a positive antinuclear antibody titer (Wright, 2007). The most important complication is visual loss with significant visual impairment in 3% to 66% of JIA patients who develop uveitis (Sabri, 2008). Without early detection and aggressive therapy, the uveitis and topical steroid therapy used to treat it may result in cataracts, glaucoma, and even blindness. A variety of systemically administered anti-inflammatory agents have been found useful for the treatment of JIA-associated uveitis. Methotrexate is often the first line disease modifying systemic agent used to help wean topical corticosteroids, but when ineffective, a variety of other systemic agents have shown promising results in refractory JIA-associated uveitis (Wright, 2007).

Plaque Psoriasis

Psoriasis is a common chronic skin disease that comes in different forms and varying levels of severity. Most researchers now conclude that it is related to the immune system (psoriasis is often called an "immune-mediated" disorder). It is not contagious. In general, it is a condition that is frequently found on the knees, elbows, scalp, hands, feet or lower back. Many treatments are available to help manage its symptoms. More than 4.5 million adults in the United States have psoriasis and between 10 percent and 30 percent of those afflicted also develop a related form of arthritis, called psoriatic arthritis.

Psoriatic Arthritis

Psoriatic arthritis is a rheumatoid-like arthritis associated with psoriasis of the skin and nails and a negative test for rheumatoid factor; HLA B27 antigen is present in some patients, especially when the spine is involved. Psoriatic arthritis affects men and women of all races and usually occurs between the ages of 20 and 50, but can occur at any age. Treatment is directed at controlling skin lesions and joint inflammation. Drug therapy is similar to that for RA, except for antimalarials, which are of only mild benefit.

Rheumatoid Arthritis

Rheumatoid arthritis affects 2.1 million Americans, usually between the ages of 20 and 60. Adults in their mid to late fifties are especially vulnerable. Rheumatoid arthritis is three times as prevalent in women than in men. Arthritis and related musculoskeletal conditions such as rheumatoid arthritis cost the U.S. economy nearly \$125 billion per year in medical care and indirect expenses such as lost wages and production. The traditional pharmacologic approach to RA consists of NSAIDs to reduce pain, swelling, and inflammation, plus a DMARD, such as methotrexate, hydroxychloroquine (an antimalarial), sulfasalazine, gold salts, d-penicillamine, azathioprine, or cyclosporine, to slow the course of the disease and prevent joint and cartilage destruction.

Professional Organization Guidelines and Recommendations

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The American Academy of Dermatology has approved a set of evidence-based guidelines, *Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis* (AAD, 2008), intended to assist physicians in managing the complexities of the treatment of individuals with psoriasis and psoriatic arthritis. The two published guidelines include: *Section 1: Overview of Psoriasis and Guidelines of Care for the Treatment of Psoriasis with Biologics* (Menter, 2008), and *Section 2: Psoriatic Arthritis: Overview and Guidelines of Care for Treatment with an Emphasis on the Biologics* (Gottlieb, 2008). According to the AAD, the first set of guidelines provides an overview of psoriasis classification, co-morbidities, assessment tools, and the use of biologics to treat psoriasis. The second set of guidelines is intended to assist dermatologists in arriving at an early diagnosis of psoriatic arthritis. It states, “Although patients with mild to moderate psoriatic arthritis may be treated with nonsteroidal anti-inflammatory drugs and/or intra-articular steroid injections, the use of disease-modifying antirheumatic drugs, particularly methotrexate, along with the biologic agents, are considered the standard of care in patients with more significant psoriatic arthritis” (AAD, 2008; Gottlieb, 2008).

The American College of Rheumatology *2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis* focuses on “the nonbiologic and biologic therapies for the treatment of RA on the background of optimal and appropriate use on nonmedical therapies as well as anti-inflammatory pharmacologic interventions. The recommendations developed focus on the initiation of drug therapies or indications to resume drug therapy in RA.” Included with these recommendations are therapeutic contraindications derived “primarily from observational studies, and to a lesser degree from evidence from randomized controlled trials.” Safety monitoring, risk surveillance, and recommendations for vaccinations in patients with RA receiving nonbiologic and biologic DMARDs are also addressed in this document (ACR, 2008; Saag, 2008).

In 2001, a clinical practice guideline, *Management of Crohn’s Disease in Adults*, was developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee. This guideline offers general management and therapeutic recommendations for Crohn’s disease in adults that “depend upon the disease location, severity, and complications. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Therapy is sequential to treat “acute disease” and then to “maintain remission.” Surgery is advocated for obstructing stenoses, suppurative complications, or medically intractable disease. Narcotic analgesia should be avoided except for the perioperative setting because of the potential for tolerance and abuse in the setting of chronic disease.” In addition, the document states there are “many unresolved questions regarding practice guidelines for Crohn’s disease because of insufficient data and experience to make recommendations.” Despite the existence of these “controversial issues,” the primary objective of medical management for Crohn’s disease is to restore the patient to health and well-being (Hanauer, 2001).

Definitions

Crohn’s disease (CD): an idiopathic, inflammatory bowel disease (IBD) characterized by discontinuous, transmural inflammation located anywhere in the gastrointestinal tract from the mouth to the anus

Fistulizing: the formation of an abnormal passage from one epithelialized surface to another

Induction: treatment designed as a first step toward treatment of a given condition

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Juvenile idiopathic arthritis (JIA) (previously known as juvenile rheumatoid arthritis or JRA): a form of rheumatoid arthritis in children that generally occurs prior to the age of 16, favors one or more large joints and can interfere with normal bone growth

Monoclonal antibody: monoclonal antibodies are produced by a single clone of cells and are of exceptional purity and specificity

Psoriasis: a chronic autoimmune skin disease that is characterized by circumscribed red patches covered with white scales

Refractory: resistant to ordinary treatment

Rheumatoid arthritis (RA): a chronic inflammatory disease characterized by symmetrical joint involvement, which causes pain, swelling, stiffness, and loss of function in the joints

Seronegative: producing a negative reaction to serological tests

Spondyloarthropathy: the spondyloarthropathies (SpA) are a heterogeneous set of disorders which include ankylosing spondylitis and psoriatic arthritis characterized by axial skeletal involvement and frequent association with the HLA B27 antigen

Tumor necrosis factor (TNF or TNF- α): a naturally occurring cytokine that is involved in normal inflammatory and immune responses

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

HCPCS

C9249	Injection, certolizumab pegol, 1 mg (Cimzia)
J0135	Injection, adalimumab, 20 mg (Humira)
J1438	Injection, etanercept; 25 mg (when drug administered under the direct supervision of a physician, not for use when drug is self administered) (Enbrel)
J1745	Injection, infliximab; 10 mg (Remicade)
S9359	Home infusion therapy, antitumor necrosis factor intravenous therapy; (e.g., Infliximab); per diem

ICD-9 Diagnosis

555.0-555.2	Regional enteritis (Crohn's disease) – (Remicade, Humira, Cimzia)
555.9	Regional enteritis, unspecified site – (Remicade, Humira, Cimzia)
556.0-556.9	Ulcerative colitis - (Enbrel, Remicade)
569.81	Fistula of intestine, excluding rectum and anus – (Remicade)
619.1	Digestive-genital tract fistula, female (rectovaginal fistula) – (Remicade)

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696.0	Psoriatic arthropathy – (Enbrel, Remicade, Humira)
696.1	Psoriasis – (Enbrel, Remicade, Humira)
714.0-714.2	Rheumatoid arthritis (Enbrel, Remicade, Humira)
714.30-714.31	Polyarticular juvenile rheumatoid arthritis – (Enbrel, Humira)
720.0-720.9	Ankylosing spondylitis and other inflammatory spondylopathies – (Enbrel, Remicade and Humira)

When services are Not Medically Necessary:

For the procedure and diagnosis codes listed above, in situations described in the Position Statement section as not medically necessary.

When services are Investigational and Not Medically Necessary:

For the procedure and diagnosis codes listed above, when criteria are not met, for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

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Tumor Necrosis Factor Antagonists

TST
 Tumor Necrosis Factor Antagonist
 Ulcerative Colitis
 Uveitis

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	04/01/2009	Updated coding section with 04/01/2009 HCPCS changes.
Revised	02/26/2009	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised dose escalation and maintenance dose information for infliximab (Remicade) for pediatric Crohn’s disease (more frequent than the FDA label indication). Updated rationale, discussion and references to address: 1) off-FDA label indication of infliximab for JIA-related uveitis; 2) updated etanercept (Enbrel) and certolizumab pegol (Cimzia) labels.
Revised	11/20/2008	MPTAC review. Aligned not medically necessary statements to CG-DRUG-12 for the TNF antagonists. Clarified language for use of TNF antagonists as not medically necessary if the patient is not tested with a TST or a CDC-recommended equivalent to rule out latent Tb. Defined conventional therapies in the ulcerative colitis medically necessary statement. Updated background/overview re: 1) use of TNF antagonists during pregnancy and lactation; 2) FDA alert and boxed warnings for the increased risk of potentially life-threatening, opportunistic fungal infections while on TNF antagonists; and, 3) recommendation for updating vaccination status of pediatric Crohn’s disease and JIA patients prior to initiation of TNF antagonists, and, not medically necessary indication of concurrent administration of live vaccines with TNF antagonists. Updated definitions and references.
Revised	08/28/2008	MPTAC review. Revised investigational and not medically necessary indications for infliximab (Remicade) and etanercept (Enbrel) to address specific off-label conditions. Reformatted adalimumab (Humira) medically necessary criteria. Revised dosing information based on FDA labels for etanercept (Enbrel) for adult RA, ankylosing spondylitis, and psoriatic arthritis (50 mg dose can be given as two 25 mg SC injections in one day or 3 or 4 days apart) and added combination therapy statement. Addition of etanercept (Enbrel) induction dosing information for adult plaque psoriasis. Revised maintenance dosing information to include administration every 6 (more frequent than the FDA label) to 8 weeks for infliximab (Remicade) for adult psoriatic arthritis and plaque psoriasis. Expanded rationale to include investigational and not medically necessary off-label conditions. Addition of an FDA boxed warning (June 4, 2008) concerning the development of lymphomas and other cancers in children and young adults. Addition of professional organization guidelines and recommendations for use of TNF antagonists. Updated references.

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Tumor Necrosis Factor Antagonists

Status	Date	Action
Revised	05/15/2008	MPTAC review. Addition of medically necessary criteria to include the FDA-approved use of certolizumab pegol (Cimzia) for the treatment of Crohn’s disease in adults with moderately to severely active disease who have had an inadequate response to conventional therapies. Addition of not medically necessary and investigational and not medically necessary criteria for certolizumab (Cimzia). For etanercept (Enbrel), revised juvenile idiopathic arthritis (JIA) medically necessary criteria for pediatric patients with moderately to severely active polyarticular disease to expand age to 2 years and older. Black box warning discussion added to etanercept (Enbrel) regarding the risk of infections and tuberculosis. For infliximab (Remicade) and etanercept (Enbrel), removed/deleted the medically necessary off label uses for reactive arthritis (adults) and arthritis associated with inflammatory bowel disease (adults). Addition of not medically necessary statement to all TNF antagonists for concurrent administration of live vaccines. Updated examples of conventional therapies for Crohn’s disease for consistency with CG-DRUG-17. Updated rationale, background, dosing information, definitions, coding and references.
Revised	02/29/2008	MPTAC review. Revised medically necessary criteria to include new FDA-approved use of adalimumab (Humira) for the treatment of moderately to severely active polyarticular juvenile idiopathic arthritis in patients four years of age and older.
Revised	02/21/2008	MPTAC review. Revised medically necessary criteria to include new FDA-approved use of adalimumab for the treatment of individuals 18 and older with moderate to severe chronic plaque psoriasis. Modified language in medically necessary indication for infliximab (Remicade) and etanercept (Enbrel) for psoriatic arthritis and plaque psoriasis to more closely match language in CG-DRUG-12. Updated review date, dosing information, rationale, coding, references and history sections.
Revised	11/29/2007	MPTAC review. Changed dosing frequency for Infliximab (Remicade) for adults with GI disorders from every 8 weeks to every 6 weeks if there is drug failure when being given every 8 weeks. Noted that dosing change is more frequent than FDA labeled use. The phrase “investigational/not medically necessary” was clarified to read “investigational and not medically necessary.” Updated coding section.
Revised	03/08/2007	MPTAC review. Addition of Humira for treatment of Crohn’s disease as approved by the FDA.
Revised	12/07/2006	MPTAC review. Addition of Remicade for treatment of chronic extensive or disabling plaque psoriasis as approved by the FDA. Addition of Remicade for treatment of ulcerative colitis including as maintenance therapy as approved by the FDA. Addition of Humira for inhibiting the progression of structural damage and improving physical function in patients with psoriatic arthritis as approved by the FDA. Addition of usage of another immunosuppressive instead of methotrexate with Remicade for rheumatoid arthritis with methotrexate intolerance.
Revised	09/14/2006	MPTAC review. Addition of Humira for treatment of ankylosing spondylitis as

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Coverage Guideline

DRUG.00002

Tumor Necrosis Factor Antagonists

Status	Date	Action
Revised	06/08/2006	approved by FDA. Review and update safety indications. Addition of dosage chart per product information. Extensive literature review. MPTAC review. Change to title. Removal of Biologic Response Modifiers and placement of Kineret (anakinra) into Pharmacology Toolkit. Update to references. Inclusion of black box warning for Remicade to include Hepatosplenic T-Cell Lymphoma in adolescent and young adult patients. Change to labeled indication for Remicade for Crohn's Disease to include pediatric patients greater than or equal to 6 years of age.
Revised	12/01/2005	MPTAC review. Addition of FDA approval of Humira.
Revised	09/22/2005	MPTAC review. Position Statement: Removed indication of etanercept (Enbrel) as first-line treatment for psoriatic arthritis before use of Infliximab (Remicade). Provided clarification of off label use of Infliximab (Remicade) for arthritis associated with inflammatory bowel disease. Noted that additional specific patient selection criteria for use for psoriatic arthritis and plaque psoriasis may apply for Infliximab (Remicade) and Etanercept (Enbrel).
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization. Updated coding: Added HCPCS code J0135; added ICD-9 Diagnoses codes 714.0-714.2, 714.30, 720.0-720.9

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	04/28/2004	DRUG.00002	Tumor Necrosis Factors and Biologic Response Modifiers
WellPoint Health Networks, Inc.	12/02/2004	Pharmacology Toolkit	Infliximab (Remicade)

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