CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Effective Date **7/15/2011**
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Coverage Policy Number **4062**

Subject **Adalimumab (Humira®)**

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Hyperlink to Related Coverage Policies

Actemra®
Cimzia®
Enbrel®
Kineret®
Orencia®
Remicade®
Rituxan®
Simponi™

INSTRUCTIONS FOR USE

*Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA*

Coverage Policy

CIGNA covers adalimumab (Humira®) as medically necessary for the treatment of ANY of the conditions listed when the associated criteria are met:

- active rheumatoid arthritis (RA) in adults for **EITHER** of the following indications:
  - history of a beneficial clinical response to adalimumab
  - inadequate response, intolerance, or contraindication to at least one disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Leflunomide, Penicillamine, Sulfasalazine)

- polyarticular juvenile idiopathic arthritis (JIA) in a child 4 years of age and older for **EITHER** of the following indications:
  - history of a beneficial clinical response to adalimumab
  - inadequate response, intolerance, or contraindication to at least one disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Penicillamine, Sulfasalazine)

- psoriatic arthritis **AND EITHER** of the following:

- history of beneficial clinical response to adalimumab
- failure, contraindication, or intolerance to methotrexate therapy

- ankylosing spondylitis **AND EITHER** of the following:
  - history of beneficial clinical response to adalimumab
  - failure, contraindication, or intolerance to non-steroidal anti-inflammatory drugs (NSAIDs)

- active Crohn's disease **AND ANY** of the following:
  - history of beneficial clinical response to adalimumab
  - failure, inadequate response, contraindication or intolerance to conventional therapies (aminosalicylate, corticosteroids, or immumomodulators)

- chronic plaque psoriasis in an adult **AND EITHER** of the following:
  - history of beneficial clinical response to adalimumab
  - individual has a failure, contraindication, or intolerance to **ANY** of the following:
    - Systemic therapy (e.g., methotrexate, cyclosporin, soriatane)
    - Phototherapy [narrow or broad band ultraviolet B (UVB), or psoralen plus ultraviolet A (PUVA)]
    - Topical therapy (e.g., coal tar, keratolytics, corticosteroids, anthralin, dovonex, tazorac)

The dosage, frequency, site of administration, and duration of therapy are reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to adalimumab (Humira®) therapy.

FDA Approved Indications

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

Rheumatoid Arthritis (RA)
Used alone or in combination with methotrexate or other disease-modifying anti-rheumati drugs (DMARDs), to reduce signs and symptoms, including major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease

Juvenile Idiopathic Arthritis (JIA)
Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 4 years of age and older. Adalimumab can be used alone or in combination with methotrexate.

Psoriatic Arthritis
Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function

Ankylosing Spondylitis
Reducing signs and symptoms in patients with active disease

Crohn's Disease
Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Plaque Psoriasis
For the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate.

FDA Recommended Dosing

Adult Patients with Rheumatoid Arthritis (RA), Psoriatic Arthritis, or Ankylosing Spondylitis
40 mg administered every other week as a subcutaneous injection.

JIA in patients 4 to 17 years of age
Based on weight as follows: pediatric patients (4 to 17 years) dose 15 kg (33 lbs) to <30 kg (66 lbs) - 20 mg every other week (20 mg prefilled syringe); ≥30 kg (66 lbs) - 40 mg every other week (HUMIRA Pen or 40 mg prefilled syringe). Limited data are available for adalimumab treatment in pediatric patients with a weight below 15 kg (33 lbs).

Crohn's Disease
160 mg initially on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later. Two weeks later begin a maintenance dose of 40 mg every other week. Aminosalicylates and/or corticosteroids may be continued during treatment. Azathioprine, 6-mercaptopurine (6-MP) or MTX may be continued during treatment if necessary. The use of Humira in Crohn's disease beyond one year has not been evaluated in controlled clinical studies.

Chronic Plaque Psoriasis
80 mg initial dose at week 0 followed by 40 mg every other week starting one week after initial dose. The use of adalimumab in moderate to severe chronic plaque psoriasis beyond one year has not been evaluated in controlled clinical studies.

Black Box Warning

SERIOUS INFECTIONS – There is an increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. Humira should be discontinued if a patient develops a serious infection or sepsis during treatment. MALIGNANCY - Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which Humira is a member. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including Humira.

Drug Availability

Adalimumab (Humira) is supplied in prefilled syringes for subcutaneous administration with the following packaging configurations:

HUMIRA Pen Carton
A carton containing two alcohol preps and two dose trays with each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe, providing 40 mg (0.8 mL) of Humira.

HUMIRA Pen – Crohn's Disease Starter Package
A carton containing 6 alcohol preps and 6 dose trays with each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe, providing 40 mg (0.8 mL) of Humira.

Prefilled Syringe Carton – 40 mg
A carton containing two alcohol preps and two dose trays with each dose tray consists of a single-dose, 1 mL prefilled glass syringe, providing 40 mg (0.8 mL) of Humira.

Pediatric Prefilled Syringe Carton - 20 mg
A carton containing two alcohol preps and two dose trays with each dose tray consists of a single-dose, 1 mL pre-filled glass syringe, providing 20 mg (0.4 mL) of Humira.

General Background

Pharmacology
Adalimumab binds specifically to TNF-alpha and blocks its interaction with the cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responsesMethotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or other disease-modifying

antirheumatic drugs (DMARDs) may be continued during treatment with adalimumab. In RA, some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency of adalimumab to 40 mg every week.

Guidelines

American College of Rheumatology (ACR)

The American College of Rheumatology (ACR) 2010 recommendations include the use of nonbiologic and biologic therapies in patients with RA when starting or resuming these therapies. The 2010 ACR recommendations address five key areas including: the indications for use, monitoring for side-effects, screening for tuberculosis which is a risk factor associated with biologic DMARDs, and off-label uses. The duration of RA disease duration, disease severity, and prognostic features were also considered when developing these recommendations. According to ACR guideline, it is important that RA patients be seen regularly to assess disease activity, evaluate disease severity, and determine whether alternative therapies are warranted. Because there was no evidence to support a specific recommendation on the frequency of provider visits, a specific and potentially arbitrary time frame is not recommended at this point. However, based on these recommendations, commonly used but not exclusive tools to assess the RA disease activity include: Disease Activity Score (DAS) in 28 joints, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Rheumatoid Arthritis Disease Activity Index, Patient Activity Scale (PAS), and Routine Assessment Patient Index Data. In addition it is recommended to use the combinations of commonly used but not exclusive prognostic factors to evaluate the patients with RA, including: Health Assessment Questionnaire (HAQ) score, Evidence of radiographic erosions, Elevated erythrocyte sedimentation rate, Elevated C-reactive protein level, and elevated levels of rheumatoid factor (RF) and/or anti– cyclic citrullinated peptide (anti-CCP) antibodies. Due to the absence of a single “gold standard” measure, multiple measures or pooled indices are used to determine a diagnosis, estimate prognosis, and to assess and monitor disease activity and response to treatment. Other commonly used measures in the clinical settings include: Visual Analogue scale (VAS), Likert scales of global response to pain by the patient/doctor, and Global Arthritis Score (GAS).

Many autoimmune rheumatic diseases have severe multisystem manifestations, including internal organ involvement and premature death. Unfortunately, for many of these conditions, standard (FDA approved) therapies do not exist, or are only effective in a subset of patients. The rarity of some of these conditions presents a barrier to performing large scale studies required for regulatory approval. However, valuable information is obtained in the published clinical reports of biologic DMARD therapies for many less common but disabling autoimmune conditions. When successful treatment options have been clearly documented in peer-reviewed journals, patients should receive the opportunity to benefit from these effective therapies.

While the American College of Rheumatology (ACR) offers a model for recommended off-label coverage criteria for use of TNF’s. Other uses where TNF products have shown efficacy of use have not been shown with this product. Therefore, any other use for this product that is not listed in the criteria coverage stem is considered experimental, investigational, and unproven.

American Academy of Dermatology (AAD)

The American Academy of Dermatology (AAD) published a consensus statement (Callen, et al., 2003) on psoriasis therapies. The document is intended to be used as a guide to the evaluation and treatments of psoriasis until evidence based guidelines are developed. Within this document, the authors state that BSA should not generally be used to determine which therapy to select; moderate and severe disease overlap and individuals with limited disease can be considered moderate for the purposes of selecting a therapy. Topical therapies are recommended for limited plaque disease. For moderate to severe disease, the AAD recommends phototherapy, targeted phototherapy, narrowband UVB, photochemotherapy with psoralen and UVA light (PUVA), topicals and systemic treatments.

Adverse Reactions

The most serious adverse effects associated with adalimumab use are reports of serious infections, rare neurologic events, and malignancies. Adalimumab carries a black box warning stating a risk of infections that have been observed, specifically tuberculosis.Therapy should not be initiated in patients with active infections (chronic or localized). Development of new infections while receiving therapy with adalimumab necessitates close monitoring. Adalimumab should be discontinued if a patient develops a serious infection. Caution is needed when considering initiation of adalimumab in patients with a history of recurrent infection, in patients

with underlying conditions predisposing to infections, or in patients geographically located where tuberculosis and histoplasmosis are widespread.

Coding/Billing Information

Note: This section is not in use.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	7/15/2008	4062	Adalimumab (Humira®)

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