



Louisiana

adalimumab (Humira[®])

Policy # 00225

Original Effective Date: 03/19/2008

Current Effective Date: 12/20/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Rheumatoid Arthritis

Based on review of available data, the Company may consider adalimumab (Humira[®])[†] for the treatment of rheumatoid arthritis (RA) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of rheumatoid arthritis (RA) when all of the following criteria are met:

- Patient has moderately to severely active rheumatoid arthritis (RA); AND
- Patient is 18 years of age or older; AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel[®])[‡] OR other drugs such as tofacitinib (Xeljanz/XR[®])[‡] or apremilast (Otezla[®])[‡]; AND
- Patient has failed treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs); AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

Note:

The recommended dosing of adalimumab (Humira) in rheumatoid arthritis (RA) is 40 mg every other week. Members unresponsive to 40 mg every other week after 12 weeks of therapy AND NOT on Methotrexate (MTX) may be approved for 40 mg once weekly dosing.

Polyarticular Juvenile Idiopathic Arthritis

Based on review of available data, the Company may consider adalimumab (Humira) for the treatment of polyarticular juvenile idiopathic arthritis (PJIA) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of polyarticular juvenile idiopathic arthritis (PJIA) when all of the following criteria are met:

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- Patient is 2 years of age or older with moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA); AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla); AND
- Patient has failed treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs); AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

Psoriatic Arthritis

Based on review of available data, the Company may consider adalimumab (Humira) for the treatment of psoriatic arthritis (PsA) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of psoriatic arthritis (PsA) when all of the following criteria are met:

- Patient is 18 years of age or older; AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla); AND
- Patient has failed treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs); AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

Ankylosing Spondylitis

Based on review of available data, the Company may consider adalimumab (Humira) for the treatment of active ankylosing spondylitis (AS) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of active ankylosing spondylitis (AS) when all of the following criteria are met:

- Patient is 18 years of age or older; AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla); AND

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- Patient has failed treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or has documented contraindications to non-steroidal anti-inflammatory drugs (NSAIDs) usage; AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

Crohn's Disease

Based on review of available data, the Company may consider adalimumab (Humira) for the treatment of Crohn's disease (CD) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of Crohn's disease (CD) when all of the following criteria are met:

- Patient is 18 years of age or older; AND
- Patient has moderately to severely active Crohn's disease (CD); AND
- Patient has failed treatment with conventional therapies such as corticosteroids, 6-mercaptopurine (6 MP) or azathioprine; AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla); AND
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

Pediatric Crohn's Disease

Based on review of available data, the Company may consider adalimumab (Humira) for the treatment of pediatric Crohn's disease (CD) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of pediatric Crohn's disease (CD) when all of the following criteria are met:

- Patient is 6 years of age or older; AND
- Patient has moderately to severely active Crohn's disease (CD); AND
- Patient has failed treatment with conventional therapies such as corticosteroids or immunosuppressants, such as 6-mercaptopurine (6 MP), methotrexate (MTX), or azathioprine; AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla); AND
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

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Plaque Psoriasis

Based on review of available data, the Company may consider adalimumab (Humira) for the treatment of plaque psoriasis to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of plaque psoriasis when all of the following criteria are met:

- Patient is 18 years of age or older; AND
- Patient has moderate to severe chronic plaque psoriasis; AND
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment; AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla); AND
- Greater than 10% of body surface area (BSA) or less than or equal to 10% BSA with plaque psoriasis involving sensitive areas or areas that would significantly impact daily function (such as palms, soles of feet, head/neck or genitalia); AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has failed to respond to an adequate trial of one of the following treatment modalities:
 - o Ultraviolet B; or
 - o Psoralen positive Ultraviolet A; or
 - o Systemic therapy (i.e., methotrexate [MTX], cyclosporine, acitretin).

*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

Ulcerative Colitis

Based on review of available data, the Company may consider adalimumab (Humira) for the treatment of ulcerative colitis (UC) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of ulcerative colitis (UC) when all of the following criteria are met:

- Patient is 18 years of age or older; AND
- Patient has moderately to severely active ulcerative colitis (UC); AND
- Patient has failed treatment with conventional therapies such as corticosteroids, azathioprine, or 6-mercaptopurine (6-MP); AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla); AND

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- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

Hidradenitis Suppurativa

Based on review of available data, the Company may consider adalimumab (Humira) for the treatment of hidradenitis suppurativa (HS) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of hidradenitis suppurativa (HS) when all of the following criteria are met:

- Patient has moderate to severe hidradenitis suppurativa (HS); AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla); AND
- Patient has failed treatment with ONE other therapy (e.g., intralesional or oral corticosteroids, systemic antibiotics, isotretinoin) for hidradenitis suppurativa (HS); AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

Uveitis

Based on review of available data, the Company may consider adalimumab (Humira) for the treatment of uveitis in adults to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for adalimumab (Humira) for the treatment of uveitis when all of the following criteria are met:

- Patient has a diagnosis of non-infectious intermediate uveitis, non-infectious posterior uveitis, or non-infectious panuveitis; AND
- Patient is 18 years of age or older; AND
- Humira is NOT used in combination with other biologic disease-modifying anti-rheumatic drugs (DMARDs), such as etanercept (Enbrel) OR other drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla); AND
- Patient has failed treatment with ONE other therapy for this condition (e.g. corticosteroids or immunosuppressive drugs); AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of adalimumab (Humira) when patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****), OR for use in any other indication than those listed above to be **investigational**.*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of adalimumab (Humira) when any of the following criteria for their respective disease listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary****:

- For rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA), and psoriatic arthritis (PsA):
 - Patient has failed treatment to one or more disease-modifying anti-rheumatic drugs (DMARDs)
- For ankylosing spondylitis (AS):
 - Patient has failed treatment with non steroidal anti-inflammatory drugs (NSAIDs) or has documented contraindications to non steroidal anti-inflammatory drugs (NSAIDs) usage
- For plaque psoriasis:
 - Greater than 10% of body surface area (BSA) or less than or equal to 10% body surface area (BSA) with plaque psoriasis involving sensitive areas or areas that would significantly impact daily function (such as palms, soles of feet, head/neck or genitalia)
 - Patient has failed to respond to an adequate trial of one of the following treatment modalities:
 - Ultraviolet B
 - Psoralen positive Ultraviolet A
 - Systemic therapy (i.e. methotrexate [MTX], cyclosporine, acitretin)
- For hidradenitis suppurativa (HS):
 - Patient has failed treatment with ONE other therapy (e.g., intralesional or oral corticosteroids, systemic antibiotics, isotretinoin)
- For uveitis:
 - Patient has failed treatment with ONE other therapy for this condition (e.g., corticosteroids or immunosuppressive drugs).

Background/Overview

Humira (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Humira binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, juvenile idiopathic arthritis (JIA), PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that

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are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In plaque psoriasis, treatment with Humira may reduce the epidermal thickness and infiltration of inflammatory cells.

Rheumatoid Arthritis

RA is a chronic (long-term) disease that causes inflammation of the joints and surrounding tissues. It can also affect other organs. It is considered an autoimmune disease. In an autoimmune disease, the immune system confuses healthy tissue for foreign substances. Typically first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include MTX.

Polyarticular Juvenile Idiopathic Arthritis

PJIA includes the inflammation of joints and presence of arthritis in children. PJIA typically occurs in a symmetrical manner with knees, wrists, and ankles most frequently affected. However certain subgroups of children do have predominantly asymmetrical involvement. Typically first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include MTX.

Psoriatic Arthritis

PsA is an arthritis that is often associated with psoriasis of the skin. Typically first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include MTX.

Ankylosing Spondylitis

AS is a chronic inflammatory disease that affects the joints between the vertebrae of the spine, and the joints between the spine and the pelvis. It eventually causes the affected vertebrae to fuse or grow together. Nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen are used to reduce inflammation and pain associated with the condition. Corticosteroid therapy or medications to suppress the immune system may be prescribed to control various symptoms.

Crohn's Disease

CD is a chronic autoimmune disease that can affect any part of the gastrointestinal tract but most commonly occurs in the ileum. As a result of the immune attack, the intestinal wall becomes thick, and deep ulcers may form. In addition to the bowel abnormalities, CD can also affect other organs in the body. Typically, first line treatments such as corticosteroids, 6-MP and Azathioprine are used to treat this condition.

Plaque Psoriasis

Psoriasis is a common skin condition that is caused by an increase in production of skin cells. It is characterized by frequent episodes of redness, itching and thick, dry silvery scales on the skin. It is most commonly seen on the trunk, elbows, knees, scalp, skin folds and fingernails. This condition can appear suddenly or gradually and may affect people of any age; it most commonly begins between the ages of 15 and 35. Psoriasis is not contagious. It is an inherited disorder related to an inflammatory response in which the immune system produces too much TNF-alpha. It may be severe in immunosuppressed people or those who have other autoimmune disorders such as RA. Treatment is focused on control of the symptoms and prevention of secondary infections. Lesions that cover all or most of the body may be acutely painful and require hospitalization. The body loses vast quantities of fluid and becomes susceptible to severe

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secondary infections that can involve internal organs and even progress to septic shock. Typical treatments for severe cases of plaque psoriasis include ultraviolet therapy or systemic therapies such as MTX or cyclosporine.

Ulcerative Colitis

UC is a chronic, episodic, inflammatory disease of the large intestine and rectum characterized by bloody diarrhea. This disease usually begins in the rectal area and may eventually extend through the entire large intestine. Repeated episodes of inflammation lead to thickening of the wall of the intestine and rectum with scar tissue. Death of colon tissue or sepsis may occur with severe disease. The goals of treatment are to control the acute attacks, prevent recurrent attacks and promote healing of the colon. Hospitalization is often required for severe attacks. Typically, first line treatments such as corticosteroids, 6-MP and Azathioprine are used to treat this condition.

Disease-Modifying Anti-Rheumatic Drugs

DMARDs are typically used for the treatment of RA, AS, PJA, and PsA. These drugs slow the disease process by modifying the immune system.

- MTX
- Cyclosporine
- Sulfasalazine
- Mercaptopurine
- Gold Compounds

Hidradenitis Suppurativa

HS is a chronic inflammatory skin condition, also known as acne inversa. HS is a chronic, suppurative process involving the skin and subcutaneous tissues. The initial presentation of the disease typically includes recurrent, painful, and inflamed nodules. The pathogenesis of HS is somewhat unknown, but it is thought that follicular occlusion, follicular rupture, and an associated immune response appear to be important events in the clinical manifestations of this disease. HS typically occurs on intertriginous skin. The most common site is usually the axilla. Non-intertriginous skin can be affected as well. Humira is the first agent to be approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe HS. Other agents typically used for the treatment of HS include systemic antibiotics, intralesional or oral corticosteroids, or isotretinoin products.

Uveitis

Uveitis is characterized by inflammation of the uvea, which is the middle portion of the eye. Most cases are idiopathic, but identifiable causes include various infections and systemic diseases, often autoimmune. Symptoms include decreased vision, pain, redness, photophobia, and floaters. Treatment of the non-infectious type of uveitis typically includes steroids, immunosuppressants, etc. The different types of uveitis are named based on their location in the eye. Intermediate uveitis refers to inflammation localized to the vitreous humor and peripheral retina. Posterior uveitis refers to inflammation of the choroid, or the back part of the uvea. Anterior uveitis affects the front part of the eye. Panuveitis is defined as simultaneous inflammation of the anterior chamber (AC), vitreous humor, and the retina or choroid.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration

Humira (adalimumab) is currently approved for the treatment of RA, PsA, AS, JIA, UC, plaque psoriasis, CD (including pediatric CD), HS, and non-infectious uveitis.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Rheumatoid Arthritis

The efficacy and safety of Humira were assessed in five randomized, double-blind studies in patients ≥ 18 years of age with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Humira was administered subcutaneously (SC) in combination with MTX (12.5 to 25 mg, Studies RA-I, RA-III and RA-V) or as monotherapy (Studies RA-II and RA-V) or with other DMARDs (Study RA-IV). The results of Study RA-I were similar to Study RA-III; patients receiving Humira 40 mg every other week in Study RA-I also achieved ACR 20, 50 and 70 response rates of 65%, 52% and 24%, respectively, compared to placebo responses of 13%, 7% and 3% respectively, at 6 months ($p < 0.01$). In Study RA-IV, 53% of patients treated with Humira 40 mg every other week plus standard of care had an ACR 20 response at week 24 compared to 35% on placebo plus standard of care ($p < 0.001$). In Study RA-V with MTX naïve patients with recent onset RA, the combination treatment with Humira plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or Humira monotherapy at Week 52 and responses were sustained at Week 104. Humira/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Polyarticular Juvenile Idiopathic Arthritis

The safety and efficacy of Humira were assessed in a multicenter, randomized, withdrawal, double-blind, parallel-group study in 171 children (4 to 17 years of age) with PJIA. The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomized withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, Humira was administered based on BSA at a dose of 24 mg/m² up to a maximum total body dose of 40 mg SC every other week. In the OLE-FD phase, the patients were treated with 20 mg of Humira SC every other week if their weight was less than 30 kg and with 40 mg of Humira SC every other week if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or prednisone (≤ 0.2 mg/kg/day or 10 mg/day maximum). At the end of the 16-week OL-LI phase, 94% of the patients in the MTX stratum and 74% of the patients in the non-MTX stratum were Pediatric ACR 30 responders. In the double-blind phase significantly fewer patients who received Humira experienced disease flare compared to placebo, both without MTX (43% vs. 71%) and with MTX (37% vs. 65%). More patients treated with Humira continued to show pediatric ACR 30/50/70 responses at Week 48

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compared to patients treated with placebo. Pediatric ACR responses were maintained for up to two years in the OLE phase in patients who received Humira throughout the study.

Humira was assessed in an open-label, multicenter study in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with moderately to severely active PJIA. Most patients (97%) received at least 24 weeks of Humira treatment dosed 24 mg/m² up to a maximum of 20 mg every other week as a single SC injection up to a maximum of 120 weeks duration. During the study, most patients used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs. The primary objective of the study was evaluation of safety.

Psoriatic Arthritis

The safety and efficacy of Humira was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with PsA. Compared to placebo, treatment with Humira resulted in improvements in the measures of disease activity. Similar responses were seen in patients with each of the subtypes of PsA, although few patients were enrolled with the arthritis mutilans and AS-like subtypes. Patients with psoriatic involvement of at least three percent BSA were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the Humira group (N=69), compared to 1% and 0% respectively, in the placebo group. Humira-treated patients demonstrated greater inhibition of radiographic progression compared to placebo-treated patients and this effect was maintained at 48 weeks. In Study PsA-I, physical function and disability were assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 40 mg of Humira every other week showed greater improvement from baseline in the HAQ-DI score (mean decreases of 47% and 49% at Weeks 12 and 24 respectively) in comparison to placebo (mean decreases of 1% and 3% at Weeks 12 and 24 respectively). At Weeks 12 and 24, patients treated with Humira showed greater improvement from baseline in the SF-36 Physical Component Summary score compared to patients treated with placebo, and no worsening in the SF-36 Mental Component Summary score.

Ankylosing Spondylitis

The safety and efficacy of Humira 40 mg every other week was assessed in 315 adult patients in a randomized, 24 week double-blind, placebo-controlled study in patients with active AS who had an inadequate response to glucocorticoids, NSAIDs, analgesics, MTX or sulfasalazine. The blinded period was followed by an open-label period during which patients received Humira 40 mg every other week SC for up to an additional 28 weeks. Improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks. At 12 weeks, the Ankylosing Spondylitis Assessment (ASAS) 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving Humira, compared to 21%, 10%, and 5% respectively, of patients receiving placebo (p <0.001). Similar responses were seen at Week 24 and were sustained in patients receiving open-label Humira for up to 52 weeks.

Crohn's Disease

The safety and efficacy of multiple doses of Humira were assessed in adult patients with moderately to severely active CD in randomized, double-blind, placebo-controlled studies. Induction of clinical remission

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(defined as Crohn's Disease Activity Index [CDAI] < 150) was evaluated in two studies. In Study CD-I, 299 TNF-blocker naïve patients were randomized to one of four treatment groups: the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg Humira at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2. Clinical results were assessed at Week 4. In the second induction study, Study CD-II, 325 patients who had lost response to, or were intolerant to, previous infliximab therapy were randomized to receive either 160 mg of Humira at Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4. A greater percentage of the patients treated with 160/80 mg Humira achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF blocker naïve (CD-I), or had lost response to or were intolerant to infliximab.

Maintenance of clinical remission was evaluated in Study CD-III. In this study, 854 patients with active disease received open-label Humira 80 mg at week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg Humira every other week, 40 mg Humira every week, or placebo. The total study duration was 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4. In Study CD-III at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. At Weeks 26 and 56, greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the Humira 40 mg every other week maintenance group compared to patients in the placebo maintenance group. The group that received Humira therapy every week did not demonstrate significantly higher remission rates compared to the group that received Humira every other week.

Ulcerative Colitis

The safety and efficacy of Humira were assessed in adult patients with moderately to severely active UC despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP in two randomized, double-blind, placebo-controlled clinical studies (Studies UC-I and UC-II). Induction of clinical remission at Week 8 was evaluated in both studies. Clinical remission at Week 52 and sustained clinical remission (defined as clinical remission at both Weeks 8 and 52) were evaluated in Study UC-II. In both Studies UC-I and UC-II, a greater percentage of the patients treated with 160/80 mg of Humira compared to patients treated with placebo achieved induction of clinical remission. In Study UC-II, a greater percentage of the patients treated with 160/80 mg of Humira compared to patients treated with placebo achieved sustained clinical remission (clinical remission at both weeks 8 and 52).

Plaque Psoriasis

The safety and efficacy of Humira were assessed in randomized, double-blind, placebo controlled studies (Ps-I and Ps-II) in 1696 adult patients with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy. The studies evaluated the proportion of patients who achieved "clear" or "minimal" disease on the 6-point Physician's Global Assessment (PGA) scale and the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16. At week 16 In PS-I, 4% of patients in the placebo group vs. 62% in the Humira 40mg every other week group had a PGA of "clear or minimal". Seven percent of patients in the placebo group achieved a PASI 75 vs. 71% in the Humira group. At week 16 in Ps-II 10% of patients in the placebo group vs. 71% in

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the Humira 40mg every other week group had a PGA of “clear or minimal”. Nineteen percent of patients in the placebo group achieved a PASI 75 vs. 78% in the Humira group.

Pediatric Crohn’s Disease

The safety and efficacy of Humira for pediatric patients with CD was assessed in a randomized, double-blind, 52-week clinical study in 192 pediatric patients (6 to 17 years of age). Enrolled patients had over the previous two year period an inadequate response to corticosteroids or an immunomodulator (i.e., azathioprine, 6-MP, or MTX). Patients who had previously received a TNF blocker were allowed to enroll if they had previously had loss of response or intolerance to that TNF blocker. Patients received open-label induction therapy at a dose based on their body weight (≥ 40 kg and < 40 kg). Patients weighing ≥ 40 kg received 160 mg (at Week 0) and 80 mg (at Week 2). Patients weighing < 40 kg received 80 mg (at Week 0) and 40 mg (at Week 2). At Week 4, patients within each body weight category (≥ 40 kg and < 40 kg) were randomized 1:1 to one of two maintenance dose regimens (high dose and low dose). The high dose was 40 mg every other week for patients weighing ≥ 40 kg and 20 mg every other week for patients weighing < 40 kg. The low dose was 20 mg every other week for patients weighing ≥ 40 kg and 10 mg every other week for patients weighing < 40 kg. Concomitant stable dosages of corticosteroids (prednisone dosage ≤ 40 mg/day or equivalent) and immunomodulators (azathioprine, 6-MP, or MTX) were permitted throughout the study. At Week 4, 28% (52/188) of patients were in clinical remission (defined as PCDAI ≤ 10). The proportions of patients in clinical remission (defined as PCDAI ≤ 10) and clinical response (defined as reduction in PCDAI of at least 15 points from baseline) were assessed at Weeks 26 and 52. At both Weeks 26 and 52, the proportion of patients in clinical remission and clinical response was numerically higher in the high dose group compared to the low dose group. The recommended maintenance regimen is 20 mg every other week for patients weighing < 40 kg and 40 mg every other week for patients weighing ≥ 40 kg. Every week dosing is not the recommended maintenance dosing regimen.

Hidradenitis Suppurativa

The safety and efficacy of Humira for patients with HS was assessed in two randomized, double-blind, placebo controlled studies in 633 adult subjects. In both studies, subjects received placebo or Humira at an initial dose of 160 mg at week 0, 80 mg at week 2, and 40 mg every week starting at week 4 through week 11. Both studies evaluated the HS Clinical Response (HiSCR) at week 12. HiSCR was defined as at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to baseline. In both studies, a higher proportion of Humira than placebo treated patients achieved HiSCR. In Study 1, 42% of subjects receiving Humira achieved the HiSCR versus 26% in the placebo group. In Study 2, 59% of subjects receiving Humira achieved the HiSCR versus 28% in the placebo group.

Uveitis

The safety and efficacy of Humira were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomized, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. The primary efficacy endpoint in both studies was ‘time to treatment failure’. Treatment failure was a multi-component outcome

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defined as the development of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, an increase in AC cell grade or vitreous haze (VH) grade or a decrease in best corrected visual acuity (BCVA). Study UV I evaluated 217 patients with active uveitis while being treated with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a standardized dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by week 15. Study UV II evaluated 226 patients with inactive uveitis while being treated with corticosteroids (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by week 19. Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with Humira versus patients receiving placebo. In both studies, all components of the primary endpoint contributed cumulatively to the overall difference between Humira and placebo groups.

References

1. American Society of Health-System Pharmacists. AHFS Drug Information 2009. Adalimumab.
2. HUMIRA Injection [package insert]. North Chicago, IL: Abbott Laboratories. Revised 09/2015.pToDate. "HS". Accessed 11/2015. www.uptodate.com

Policy History

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Current Effective Date: 12/20/2017

- 03/12/2008 Medical Director review
- 03/19/2008 Medical Policy Committee approval
- 03/04/2009 Medical Director review
- 03/18/2009 Medical Policy Committee approval. Added FDA Black Box Warning to section. No change to coverage eligibility. FDA
- 07/01/2010 Medical Policy Committee approval
- 07/21/2010 Medical Policy Implementation Committee approval. Added a *Note* stating the recommended dosing from the Humira package insert for the treatment of rheumatoid arthritis, which is 40mg every other week. The *Note* also states that those members unresponsive to this dosing after 12 weeks of therapy AND NOT on Methotrexate may be approved for 40mg once weekly dosing. Changed the verbiage of the *Note* after each set of Patient Selection Criteria to read that "all members must have a negative cancer history prior to approval", instead of a "negative cancer screening".
- 07/07/2011 Medical Policy Committee review
- 07/20/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 06/28/2012 Medical Policy Committee review
- 07/27/2012 Medical Policy Implementation Committee approval. Deleted SangCya (an international brand name) and replaced it with cyclosporine (the generic name). Added a *Note* to the criteria for rheumatoid arthritis, juvenile rheumatoid arthritis/juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis stating that patients must have failed conventional therapies specific to the condition such as NSAIDS, DMARDS, phototherapy, psoralens and hydroxyurea before using adalimumab (Humira). The reason for denial will be not medically necessary if this criterion is not met. The not medically necessary denial statement is also incorporated into the Investigational and Not Medically Necessary coverage sections. Deleted the

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	investigational statement regarding non-FDA approved indications, since it is duplicative given the additions to the coverage section.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. Added a new indication for ulcerative colitis to be eligible for coverage with criteria.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Removed the criteria under Ulcerative Colitis that the patient is unresponsive or intolerant to TNF blockers. Opened age to 4 and older on polyarticular juvenile idiopathic arthritis. Changed language for DMARD usage to match other similar policies. Changed language on therapy for plaque psoriasis to match other similar policies. Updated the investigational and not medically necessary sections. Removed the requirement for a negative cancer history.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Added a new indication for pediatric Crohn's following the package insert. Changed age to 2 years of age for polyarticular juvenile idiopathic arthritis per change of indication in package insert.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Added new indication, criteria, background, and rationale for hidradenitis suppurativa.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. Added indication of uveitis to this policy.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Clarified that this drug should not be used in combination with other biologics or other drugs like Otezla or Xeljanz/XR.
Next Scheduled Review Date:	12/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0135
ICD-10 Diagnosis	H44.131-H44.139
	K50.00-K50.019
	K50.10-K50.19
	K50.10-K50.119
	K50.80-K50.819
	K50.90-K50.919
	L40.0-L40.4
	L40.50-L40.59
	L40.8-L40.9
	L73.2
	M05.00-M05.079
	M05.09
	M05.20
	M05.211-M05.279
	M05.29-M05.30
M05.311-M05.379	
M05.39-M05.40	
M05.411-M05.479	
M05.49-M05.50	
M05.511-M05.579	
M05.59-M05.60	
M05.611-M05.679	
M05.69-M05.70	
M05.711-M05.779	
M05.79-M05.80	
M05.811-M05.879	
M05.89	
M05.9	
M06.00-M06.079	
M06.08-M06.09	
M06.1	
M06.20-M06.279	
M06.628-M06.630	
M06.311-M06.379	
M06.38-M06.39	
M06.80-M06.879	
M06.88-M06.89	
M06.9	
M08.00-M08.079	
M08.08-M08.09	
M08.1	
M08.20	
M08.211-M08.279	
M08.28-M08.29	
M08.3	
M08.40	
M08.411-M08.479	
M08.48	
M08.80	
M08.811-M08.879	
M08.88-M08.89	
M08.90	
M08.911-M08.979	
M08.98-M08.99	
M45.0-M45.9	
M48.8X1-M48.8X9	

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;

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- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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