



Medication Policy Manual

Policy No: dru444

Topic: Drugs for chronic inflammatory diseases

Date of Origin: January 8, 2016

- abatacept (Orencia®)
- adalimumab (Humira®)
- anakinra (Kineret®)
- apremilast (Otezla®)
- brodalumab (Siliq™)
- certolizumab (Cimzia®)
- etanercept (Enbrel®)
- golimumab (Simponi®, Simponi Aria®)
- guselkumab (Tremfya™)
- infliximab (Remicade®)
- infliximab-abda (Renflexis™)
- infliximab-dyyb (Inflectra®)
- ixekizumab (Taltz®)
- sarilumab (Kevzara®)
- secukinumab (Cosentyx®)
- tocilizumab (Actemra®)
- tofacitinib (Xeljanz®, Xeljanz XR)
- ustekinumab (Stelara®)
- vedolizumab (Entyvio®)

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are used to treat a group of diseases that may be caused or worsened by an overactive immune system such as rheumatoid arthritis, psoriasis, and ulcerative colitis. Administration is different for each medication, and may be a subcutaneous injection (SC), intravenous injection (IV), or administered by mouth.

Table of Contents

Policy/Criteria	3
A. Axial Spondyloarthritis (SpA) – Self-administered drugs only	3
B. Axial Spondyloarthritis (SpA) – Provider-administered drugs only	4
C. Chronic plaque psoriasis (PsO) - Self-administered drugs only	5
D. Chronic plaque psoriasis (PsO) - Provider-administered drugs only	6
E. Crohn’s disease (CD) – Self-administered drugs only.....	7
F. Crohn’s disease (CD) – Provider-administered drugs only.....	8
G. Cryopyrin-Associated Periodic Syndrome (CAPS)	9
H. Giant Cell Arteritis.....	10
I. Hidradenitis Suppurativa (HS).....	11
J. Juvenile idiopathic arthritis (JIA).....	12
K. Immune-mediated colitis.....	13
L. Psoriatic arthritis (PsA) – Self-administered medications	14
M. Psoriatic arthritis (PsA) – Provider-administered medications	15
N. Rheumatoid arthritis (RA) – Self-administered medications.....	16
O. Rheumatoid arthritis (RA) – Provider-administered medications	17
P. Systemic juvenile idiopathic arthritis (SJIA; Still's disease)	18
Q. Ulcerative colitis (UC) – Self-administered drugs only	19
R. Ulcerative colitis (UC) – Provider-administered drugs only	20
S. Uveitis.....	21
II. Administration, Quantity Limitations, and Authorization Period	22
III. Medications included in this policy are not considered medically necessary when used according to Table 2.....	22
IV. Investigational uses.....	28
Position Statement.....	35

bdDMARD:	biologic disease modifying anti-rheumatic drug (<i>etanercept, adalimumab, infliximab, certolizumab, golimumab abatacept, anakinra, apremilast, ixekizumab, secukinumab, tocilizumab, tofacitinib, ustekinumab, vedolizumab</i>)
nbDMARD:	non-biologic disease modifying anti-rheumatic drug (<i>apremilast and tofacitinib</i>)
cDMARD:	conventional disease modifying anti-rheumatic drug (<i>for example, methotrexate, sulfasalazine</i>)
TNFi:	tumor necrosis factor inhibitor(s) (<i>etanercept, adalimumab, infliximab, certolizumab, golimumab</i>)
Non-TNFi:	non-tumor necrosis factor inhibitor(s) (<i>abatacept, anakinra, apremilast, ixekizumab, secukinumab, tocilizumab, tofacitinib, ustekinumab, vedolizumab</i>)

Policy/Criteria

I. Most contracts require prior authorization approval of medications used to treat chronic inflammatory diseases prior to coverage.

A. **Axial Spondyloarthritis (SpA) – Self-administered drugs only**

1. Preferred medications may be considered medically necessary when criterion a is met.
2. Non-preferred medications may be considered medically necessary when criteria a and b below are met.

Preferred	adalimumab (Humira), certolizumab (Cimzia), golimumab (Simponi)
Non-preferred	etanercept (Enbrel), secukinumab (Cosentyx)
a. A diagnosis of axial SpA, including ankylosing spondylitis (AS), is established by or in consultation with a specialist in rheumatology. AND b. (For non-preferred drugs only) There is clinical documentation that treatment with at least two preferred biologic therapies is not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated.	

B. Axial Spondyloarthritis (SpA) – Provider-administered drugs only

1. For provider-administered therapies, site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, *Site of Care Review*, dru408]
2. Preferred medications may be considered medically necessary when criterion a is met.
3. Non-preferred medications may be considered medically necessary when criteria a, b, and c below are met.

Preferred	certolizumab (Cimzia), infliximab (IV) (Remicade)
Non-preferred	infliximab-abda (Renflexis), infliximab-dyyb (Inflectra)
a. A diagnosis of axial SpA, including ankylosing spondylitis (AS), is established by or in consultation with a specialist in rheumatology. AND b. [For non-preferred drugs only] There is clinical documentation that treatment with at least two preferred biologic therapies is not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated. AND c. [For infliximab-abda (Renflexis) and infliximab-dyyb (Inflectra) only] There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade).	

C. Chronic plaque psoriasis (PsO) - Self-administered drugs only

1. Preferred medications may be considered medically necessary when criteria **a through d** are met.
2. Non-preferred medications may be considered medically necessary when criteria **a through e** are met.

Preferred	adalimumab (Humira), ustekinumab (Stelara)
Non-preferred	apremilast (Otezla), brodalumab (Siliq), etanercept (Enbrel), guselkumab (Tremfya), secukinumab (Cosentyx), ixekizumab (Taltz)
<p>a. A diagnosis of chronic plaque psoriasis (PsO) is established by or in consultation with a specialist in dermatology or rheumatology. AND</p> <p>b. Clinical documentation supports involvement of $\geq 10\%$ of the body surface area OR there is significant functional disability. AND</p> <p>c. Treatment with phototherapy (for example, UVB) or photochemotherapy was not effective, not tolerated, or is contraindicated (see Appendix 1). AND</p> <p>d. Treatment with at least one conventional nonbiologic response modifier (such as methotrexate) was not effective or not tolerated, unless all are contraindicated (see Appendix 2). AND</p> <p>e. <i>[For non-preferred drugs only]</i> There is clinical documentation that treatment with at least two additional preferred biologic therapies is not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated.</p>	

D. Chronic plaque psoriasis (PsO) - Provider-administered drugs only

1. For provider-administered therapies, site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, *Site of Care Review*, dru408]
2. Preferred medications may be considered medically necessary when criteria **a through d** are met.
3. Non-preferred medications may be considered medically necessary when criteria **a through f** are met.

Preferred	infliximab (Remicade), ustekinumab (Stelara)
Non-preferred	infliximab-abda (Renflexis), infliximab-dyyb (Inflectra)
<p>a. A diagnosis of chronic plaque psoriasis (PsO) is established by or in consultation with a specialist in dermatology or rheumatology.</p> <p>AND</p> <p>b. Clinical documentation supports involvement of $\geq 10\%$ of the body surface area OR there is significant functional disability.</p> <p>AND</p> <p>c. Treatment with phototherapy (for example, UVB) or photochemotherapy was not effective, not tolerated, or is contraindicated (see Appendix 1).</p> <p>AND</p> <p>d. Treatment with at least one conventional nonbiologic response modifier (such as methotrexate) was not effective or not tolerated, unless all are contraindicated (see Appendix 2).</p> <p>AND</p> <p>e. [For non-preferred drugs only] There is clinical documentation that treatment with at least two preferred biologic therapies is not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated.</p> <p>AND</p> <p>f. [For infliximab-abda (Renflexis) and infliximab-dyyb (Inflectra) only] There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade)</p>	

E. Crohn's disease (CD) – Self-administered drugs only

1. Preferred medications may be considered medically necessary when criteria a and criteria b below are met.

Preferred	adalimumab (Humira), certolizumab (Cimzia), ustekinumab (Stelara)
<p>a. A diagnosis of Crohn's disease (CD) is established by or in consultation with a specialist in gastroenterology</p> <p>AND</p> <p>b. Criteria i, or ii. below are met:</p> <p>i. Fistulizing Crohn's disease.</p> <p>OR</p> <p>ii. Acute treatment of an exacerbation when at least one of the criteria 1 through 3 below, is met.</p> <p>1. Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) has been ineffective or is contraindicated.</p> <p>OR</p> <p>2. The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease.</p> <p>OR</p> <p>3. The patient is experiencing breakthrough disease (e.g. active disease flares) while stabilized for at least 2 months on a cDMARD (see Appendix 2).</p>	

F. Crohn's disease (CD) – Provider-administered drugs only

1. For provider-administered therapies, site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, *Site of Care Review*, dru408]
2. Preferred medications may be considered medically necessary when criteria a and b are met.
3. Non-preferred medications may be considered medically necessary when criteria a and c below are met.
4. Infliximab (Infliximab) may be considered medically necessary when criteria a, c, and d below are met.

Preferred	infliximab (Remicade), certolizumab (Cimzia), ustekinumab (Stelara)
Non-preferred	infliximab-abda (Renflexis), infliximab-dyyb (Infliximab), vedolizumab (Entyvio),
<p>a. A diagnosis of Crohn's disease (CD) is established by or in consultation with a specialist in gastroenterology</p> <p>AND</p> <p>b. Criteria i or ii below are met:</p> <p style="padding-left: 20px;">i. Fistulizing Crohn's disease.</p> <p style="text-align: center;">OR</p> <p style="padding-left: 20px;">ii. Acute treatment of an exacerbation when at least one of the criteria 1 through 3 below, is met.</p> <p style="padding-left: 40px;">1. Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) has been ineffective or is contraindicated.</p> <p style="text-align: center;">OR</p> <p style="padding-left: 40px;">2. The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease.</p> <p style="text-align: center;">OR</p> <p style="padding-left: 40px;">3. The patient is experiencing breakthrough disease (e.g. active disease flares) while stabilized for at least 2 months on a cDMARD (see Appendix 2).</p> <p>AND</p> <p>c. <i>[For non-preferred medications only]</i> There is clinical documentation that both adalimumab (Humira) and infliximab (Remicade) are not effective after at least an initial three-dose induction period unless it is not tolerated.</p> <p>AND</p> <p>d. <i>[For infliximab-abda (Renflexis) and infliximab-dyyb (Infliximab) only]</i> There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade)</p>	

G. Cryopyrin-Associated Periodic Syndrome (CAPS)

Anakinra (Kineret) may be considered medically necessary when criteria 1 through 3, below, are met

1. A diagnosis of **Cryopyrin-Associated Periodic Syndromes (CAPS)** including **Neonatal-Onset Multisystem Inflammatory Disease (NOMID)** when established by or in consultation with a specialist in rheumatology.

AND

2. There is laboratory evidence of a genetic mutation in the Cold-induced Auto-inflammatory Syndrome 1 (CIAS1; sometimes referred to as the NLRP-3) gene.

AND

3. There is clinical documentation of at least one of i through iii below.
 - a. NOMID – Urticaria-like rash, central nervous system involvement [e.g. papilledema, cerebrospinal fluid (CSF) pleocytosis, or sensorineural hearing loss], elevated C-reactive protein, or epiphyseal and/or patellar overgrowth on radiographs.

OR

- b. Familial Cold Auto-inflammatory Syndrome (FCAS) – Recurrent intermittent episodes of fever and rash that primarily follow natural, artificial (e.g. air conditioning), or both types of generalized cold exposure.

OR

- c. Muckle-Wells Syndrome (MWS) – Syndrome of chronic fever and rash that may wax and wane in intensity and may be exacerbated by generalized cold exposure. This syndrome may be associated with deafness or amyloidosis.

H. Giant Cell Arteritis

Subcutaneous tocilizumab (Actemra) may be considered medically necessary when criteria 1 through 3 are met.

1. A diagnosis of giant cell arteritis is established by or in consultation with a specialist in rheumatology (see Appendix 5).

AND

2. There is documentation of that symptoms are not controlled despite treatment with high-dose glucocorticoids (prednisone 40 to 60 mg per day or equivalent, see Appendix 5), unless contraindicated or not tolerated.

I. Hidradenitis Suppurativa (HS)
Adalimumab (Humira), infliximab (Remicade), infliximab-abda (Renflexis), and infliximab-dyyb (Inflectra) may be considered medically necessary when criteria 1 through 5 are met.

1. For provider-administered therapies, site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, *Site of Care Review*, dru408]

AND

2. A diagnosis of hidradenitis suppurativa is established by or in consultation a specialist in dermatology.

AND

3. There is documentation that HS is causing pain and significant functional impairment.

AND

4. There is documentation indicating:

- i. A diagnosis of severe disease (Hurley Stage III, diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area).

OR

- ii. A diagnosis of moderate disease (Hurley Stage II, recurrent abscesses with tract and scar formation) and 12-weeks of antibiotic therapy was ineffective, unless all are not tolerated or are contraindicated. Antibiotic treatments include tetracycline, doxycycline, minocycline, erythromycin, or topical clindamycin.

AND

5. ***[For infliximab-abda (Renflexis) and infliximab-dyyb (Inflectra) only]*** There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade)

J. Juvenile idiopathic arthritis (JIA)

1. For provider-administered therapies, site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, *Site of Care Review*, dru408]
2. Adalimumab (Humira), tocilizumab (IV) (Actemra), and abatacept (IV) (Orencia) may be considered medically necessary when criteria a and b below are met.
3. Etanercept (Enbrel) may be considered medically necessary when criteria a, b, and f below are met.
4. Infliximab (Remicade) may be considered medically necessary when criteria a through d below are met.
5. Infliximab (Inflectra) may be considered medically necessary when criteria a through e below are met.

Preferred	adalimumab (Humira)
Non-preferred	tocilizumab IV (Actemra), abatacept IV (Orencia), abatacept SC (Orencia), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-dyyb (Inflectra), etanercept (Enbrel)
<p>a. Diagnosis is established by or in consultation with a specialist in rheumatology.</p> <p>AND</p> <p>b. There is clinical documentation that a cDMARD (such as methotrexate) was not effective after at least a 6 to 12 week treatment course based on one or more of the assessment components listed in Appendix 3, or that a cDMARD was not tolerated, or all cDMARDs are contraindicated (see Appendix 2).</p> <p>AND</p> <p>c. [For infliximab (Remicade only)] There is clinical documentation that treatment with two of abatacept (Orencia), adalimumab (Humira), etanercept (Enbrel), or tocilizumab (Actemra) were each not effective after at least a 12-week treatment course unless each are not tolerated or are contraindicated.</p> <p>AND</p> <p>d. [For infliximab (Remicade) and infliximab (Inflectra)] Infliximab (Remicade) is administered with a cDMARD (see Appendix 2) unless all are not tolerated or contraindicated.</p> <p>AND</p> <p>e. [For infliximab-abda (Renflexis) and infliximab-dyyb (Inflectra) only] There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade)</p> <p>AND</p> <p>f. [For etanercept (Enbrel only)] There is clinical documentation adalimumab (Humira) was not effective after at least a 12-week treatment course unless not tolerated or contraindicated.</p>	

K. Immune-mediated colitis

Infliximab (Remicade), infliximab-abda (Renflexis), or infliximab-dyyb (Inflectra) may be considered medically necessary when criteria 1 through 4 below are met.

1. Site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, *Site of Care Review*, dru408]

AND

2. A diagnosis of **colitis** due to ipilimumab (Yervoy) or an anti-PD1 agent [e.g. atezolizumab (Tecentriq), nivolumab (Opdivo), or pembrolizumab (Keytruda)]

AND

3. Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 days) has been ineffective or is contraindicated.

AND

4. ***[For infliximab-abda (Renflexis) and infliximab-dyyb (Inflectra) only]*** There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade).

L. Psoriatic arthritis (PsA) – Self-administered medications

1. Preferred medications may be considered medically necessary when criterion a is met.
2. Non-preferred medications may be considered medically necessary when criteria a and b are met.

Preferred	adalimumab (Humira), certolizumab (Cimzia), golimumab (Simponi), ustekinumab (Stelara)
Non-preferred	abatacept SC (Orencia), apremilast (Otezla), etanercept (Enbrel), secukinumab (Cosentyx)
a. A diagnosis of psoriatic arthritis (PsA) when established by or in consultation with a specialist in dermatology or rheumatology. AND b. <i>[For non-preferred medications only]</i> There is clinical documentation that treatment with two preferred biologic therapies were each not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated.	

M. Psoriatic arthritis (PsA) – Provider-administered medications

1. For provider-administered therapies, site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, *Site of Care Review*, dru408]
2. Preferred medications may be considered medically necessary when criterion a is met.
3. Non-preferred medications may be considered medically necessary when criteria a through c are met.

Preferred	certolizumab (Cimzia), infliximab (Remicade), ustekinumab (Stelara)
Non-preferred	infliximab-abda (Renflexis), infliximab-dyyb (Inflectra)
<p>a. A diagnosis of psoriatic arthritis (PsA) when established by or in consultation with a specialist in dermatology or rheumatology.</p> <p>AND</p> <p>b. [For non-preferred drugs only] There is clinical documentation that treatment with at least two preferred biologic therapies is not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated.</p> <p>AND</p> <p>c. [For infliximab-abda (Renflexis) and infliximab-dyyb (Inflectra) only] There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade)</p>	

N. Rheumatoid arthritis (RA) – Self-administered medications

1. Preferred self-administered medications may be considered medically necessary when criteria a and b are met.
2. Non-preferred self-administered medications may be considered medically necessary when criteria a through c are met.

Preferred	adalimumab (Humira), certolizumab (Cimzia), golimumab (Simponi)
Non-preferred	abatacept SC (Orencia), anakinra (Kineret), etanercept (Enbrel), tofacitinib (Xeljanz/Xeljanz XR), sarilumab (Kevzara), tocilizumab SC (Actemra)
<p>a. Diagnosis of rheumatoid arthritis (RA) established by or in consultation with a specialist in rheumatology (see Appendix 3).</p> <p>AND</p> <p>b. There is clinical documentation that a cDMARD (see Appendix 2) was not effective after at least a 6 to 12 week treatment course based on one or more of the assessment components listed in Appendix 4, or that a cDMARD was not tolerated or all cDMARDs are contraindicated.</p> <p>AND</p> <p>c. <i>[For non-preferred drugs only]</i> There is documentation that treatment with two preferred self-administered biologic therapies were each not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated.</p>	

O. Rheumatoid arthritis (RA) – Provider-administered medications

1. For provider-administered therapies, site of care administration requirements are met. [refer to *OmedaRx Medication Policy Manual, Site of Care Review, dru408*]
2. Preferred medications may be considered medically necessary when criteria, a through c are met.
3. Non-preferred medications may be considered medically necessary when criteria a, b, and d are met.
4. Infliximab (Inflectra) medications may be considered medically necessary when criteria a through e are met.

Preferred	certolizumab (Cimzia), infliximab (Remicade), golimumab (Simponi Aria)
Non-preferred	abatacept (IV) (Orencia), infliximab-abda (Renflexis), infliximab-dyyb (Inflectra), tocilizumab (IV) (Actemra)
<p>a. Diagnosis of rheumatoid arthritis (RA) established by or in consultation with a specialist in rheumatology (see Appendix 3).</p> <p>AND</p> <p>b. There is clinical documentation that a cDMARD (see Appendix 2) was not effective after at least a 6 to 12 week treatment course based on one or more of the assessment components listed in Appendix 4, or that a cDMARD was not tolerated or all cDMARDs are contraindicated.</p> <p>AND</p> <p>c. <i>[For certolizumab (Cimzia), golimumab (Simponi Aria), infliximab (Remicade), and infliximab (Inflectra)]</i> Certolizumab (Cimzia), golimumab (Simponi Aria), infliximab (Inflectra), and infliximab (Remicade) must be administered with a cDMARD (see Appendix 2) unless all are not tolerated or contraindicated.</p> <p>AND</p> <p>d. <i>[For abatacept (IV) (Orencia), infliximab-abda (Renflexis), infliximab-dyyb (Inflectra), and tocilizumab (IV) (Actemra) only]</i> There is documentation that treatment with two preferred biologic therapies were each not effective after at least a 12-week treatment course unless each were not tolerated or contraindicated.</p> <p>AND</p> <p>e. <i>[For infliximab-abda (Renflexis) and infliximab (Inflectra) only]</i> There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade)</p>	

P. Systemic juvenile idiopathic arthritis (SJIA; Still's disease)

Anakinra (Kineret) and tocilizumab (IV) (Actemra) may be considered medically necessary when criteria 1 through 4 below are met.

1. For provider-administered therapies, site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, Site of Care Review, dru408]

AND

2. A diagnosis of **systemic juvenile idiopathic arthritis** (SJIA; Still's disease) when established by or in consultation with a specialist in rheumatology

AND

3. There is disease activity greater than 6 months

AND

4. There is clinical documentation that treatment with at least one oral systemic agent (for example, methotrexate, corticosteroids) was not effective, not tolerated, or is contraindicated.

Q. Ulcerative colitis (UC) – Self-administered drugs only

1. Preferred medications may be considered medically necessary when criteria a and b below are met.

Preferred	adalimumab (Humira), golimumab SC (Simponi)
a. Diagnosis of ulcerative colitis is established by or in consultation with a specialist in gastroenterology	
AND	
b. At least one of criteria i through iii below, are met.	
i. Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) has been ineffective or is contraindicated.	
OR	
ii. Treatment with at least one aminosalicylate (for example, mesalamine, balsalazide, sulfasalazine) has been ineffective, not tolerated, or is contraindicated.	
OR	
iii. Treatment with at least one additional cDMARD (see Appendix 2) has been ineffective, not tolerated, or is contraindicated.	

R. Ulcerative colitis (UC) – Provider-administered drugs only

1. For provider-administered therapies, site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, Site of Care Review, dru408]
2. Preferred medications may be considered medically necessary when criteria a and b below are met.
3. Non-preferred medications may be considered medically necessary when criteria a and c below are met.
4. Infliximab (Infliximab) may be considered medically necessary when criteria a, c, and d below are met.

Preferred	infliximab (Remicade)
Non-preferred	infliximab-abda (Renflexis), infliximab-dyyb (Infliximab), vedolizumab (Entyvio),
<p>a. Diagnosis of ulcerative colitis is established by or in consultation with a specialist in gastroenterology</p> <p>AND</p> <p>b. [For infliximab (Remicade) only] The patient is experiencing acute exacerbation and at least one of criteria i through iii are met:</p> <ol style="list-style-type: none"> i. Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9mg/day, or budesonide rectal for 7 to 14 days) has been ineffective or is contraindicated. <p>OR</p> <ol style="list-style-type: none"> ii. The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease. <p>OR</p> <ol style="list-style-type: none"> iii. The patient is experiencing breakthrough disease (for example, active disease flares) while stabilized for at least 2 months on a cDMARD (see Appendix 2). <p>AND</p> <p>c. [For non-preferred medications only] There is clinical documentation that treatment with adalimumab (Humira) was not effective after at least an 8-week treatment course or infliximab (Remicade) was not effective after at least a 12-week treatment course, unless not tolerated or contraindicated.</p> <p>AND</p> <p>d. [For infliximab-abda (Renflexis) and infliximab-dyyb (Infliximab) only] There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade).</p>	

S. Uveitis

1. For provider-administered therapies, site of care administration requirements are met. [refer to OmedaRx Medication Policy Manual, Site of Care Review, dru408]
2. Adalimumab (Humira) may be considered medically necessary when criteria a through c are met.
3. Infliximab (Remicade) may be considered medically necessary when criteria a through d are met.
4. Infliximab (Inflectra) may be considered medically necessary when criteria a through e are met.

Preferred	adalimumab (Humira), infliximab (Remicade)
Non-preferred	infliximab-abda (Renflexis), infliximab (Inflectra)
<p>a. A diagnosis of uveitis is established by or in consultation with a specialist in ophthalmology</p> <p>AND</p> <p>b. Treatment with corticosteroids (ophthalmic or systemic) has been:</p> <ol style="list-style-type: none"> i. Ineffective after an adequate course of therapy. <p>OR</p> <ol style="list-style-type: none"> ii. Unable to be tapered following an adequate course without worsening of disease. <p>OR</p> <ol style="list-style-type: none"> iii. Not tolerated or is contraindicated. <p>AND</p> <p>c. Treatment with at least one cDMARD was not effective, not tolerated, or is contraindicated (see Appendix 2).</p> <p>AND</p> <p>d. <i>[For infliximab (Remicade) and infliximab (Inflectra) only]</i> Infliximab is administered with a cDMARD (see Appendix 2) unless all are not tolerated or contraindicated.</p> <p>AND</p> <p>e. <i>[For infliximab-abda (Renflexis) and infliximab-dyyb (Inflectra) only]</i> There is a documented intolerance or contraindication to an inactive ingredient in infliximab (Remicade).</p>	

II. Administration, Quantity Limitations, and Authorization Period

- A.** OmedaRx considers oral and subcutaneously administered drugs, with the exception of ustekinumab (Stelara) and certolizumab (Cimzia), to be self-administered (see Table 1).
- B.** OmedaRx considers intravenously administered drugs to be provider-administered medications (see Table 1).
- C.** OmedaRx considers ustekinumab (Stelara) and certolizumab (Cimzia) to be either a self-administered or provider-administered medication.
- D.** When prior authorization is approved, each drug may be covered in the following quantities and for the following authorization periods outlined in Table 1.

III. Medications included in this policy are not considered medically necessary when used according to Table 2.

Table 1. Authorization Limits

<p>Abatacept (Orencia)</p>	<p>Intravenous:</p> <ul style="list-style-type: none"> - <u>Initial authorization:</u> Maximum of 8 infusions in a 6 month period (per manufacturer labeling). - <u>Continued authorization:</u> Maximum of 13 infusions in a 1 year period based on a recommended infusion interval of every 4 weeks. - Initial authorization shall be reviewed at 6 months. - Continuous authorization or re-authorization (after the initial 6 month period) shall be reviewed at least annually, and clinical documentation indicating that there is disease stability or improvement must be provided.
	<p>Subcutaneous:</p> <ul style="list-style-type: none"> - JIA: 50 mg - 125 mg every week. - Adult PsA: 125 mg every week. - RA: 125 mg every week. A single IV loading dose may be authorized, if required. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
<p>Adalimumab (Humira)</p>	<ul style="list-style-type: none"> - axial SpA, JIA, PsA, RA: 40 mg every 2 weeks. - HS: six of the 40mg vials (240 mg) in the first month (per manufacturer labeling), then 40mg every week thereafter. - PsO and Uveitis: four of the 40 mg vials (160 mg) in the first month (per manufacturer labeling), then 40 mg every 2 weeks thereafter. - CD: Up to 12 of the 40 mg vials in the initial 3 month period (induction period), then 40 mg every 2 weeks thereafter. Up to 40 mg every week when there is clinical documentation that current treatment with adalimumab (Humira) 40 mg every 2 weeks is not effective after at least a 12 week treatment course. - UC: Up to 12 of the 40 mg vials in the initial 3 month period (induction period, per manufacturer labeling), then 40 mg every 2 weeks thereafter. - For HS: Initial authorization shall be reviewed at 12 weeks after which documentation of disease stability or clinical improvement is required for continued authorization. - For all other conditions: Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
<p>Anakinra (Kineret)</p>	<ul style="list-style-type: none"> - Up to 28 of the 100mg syringes (1 syringe dispensing pack) every 4 weeks. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
<p>Apremilast (Otezla)</p>	<ul style="list-style-type: none"> - Up to 60 tablets per 30 days. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
<p>Brodalumab (Siliq)</p>	<ul style="list-style-type: none"> - 210 mg subcutaneously at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
<p>Certolizumab</p>	<ul style="list-style-type: none"> - 10 of the 200 mg doses in the first 12 weeks of therapy, then 2 of the 200 mg doses every

(Cimzia)	<p>4 weeks thereafter.</p> <ul style="list-style-type: none"> - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
Etanercept (Enbrel)	<ul style="list-style-type: none"> - axial SpA, JIA, PsA, RA: 50 mg per week given as a single 50 mg dose weekly or 25 mg twice weekly. - PsO: up to 50 mg twice per week for the first 3 months (per manufacturer labeling), then 50 mg per week thereafter given as a single 50 mg dose weekly or 25 mg twice weekly. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
Golimumab (Simponi, Simponi Aria)	<p>Intravenous:</p> <ul style="list-style-type: none"> - <u>Initial authorization:</u> Maximum of 6 infusions in a 6 month period.. - <u>Continued authorization:</u> Maximum of 7 infusions in a 1 year period based on a recommended infusion interval of every 8 weeks. - Initial authorization shall be reviewed at 6 months. - Continuous authorization or re-authorization (after the initial 6 month period) shall be reviewed at least annually, and clinical documentation indicating that there is disease stability or improvement must be provided.
	<p>Subcutaneous:</p> <ul style="list-style-type: none"> - axial SpA, PsA, RA: A maximum of 13 syringes in a 1 year period based on a recommended injection interval of every 4 weeks. - UC: Up to 6 syringes in the initial 12-week period (induction period, 12 per manufacturer labeling), then a maximum of 13 syringes in a 1 year period based on a recommend injection interval of every 4 weeks. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
Guselkumab (Tremfya)	<ul style="list-style-type: none"> - 100 mg subcutaneously at Weeks 0 and 4 followed by 100 mg every 8 weeks thereafter. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

<p>Infliximab (Remicade), infliximab-abda (Renflexis), infliximab-dyyb (Inflixtra)</p>	<ul style="list-style-type: none"> - <u>Initial authorization:</u> <ul style="list-style-type: none"> o Immune-mediated colitis: a single-dose at 5 mg/kg o Other conditions: Up to 6 infusions in a 6-month period. - <u>Continued Authorization:</u> <ul style="list-style-type: none"> o axial SpA and HS: Maximum of 9 infusions in a 1 year period based on a <u>recommended infusion interval of every 6 weeks.</u> o PsO and PsA: Maximum of 7 infusions in a 1 year period based on a <u>recommended infusion interval of every 8 weeks.</u> o CD and UC: Maximum of 9 infusions in a 1 year period based on a <u>recommended infusion interval of every 6 weeks</u> (per manufacturer labeling). <u>A dosing interval of every 4 weeks (6 infusions in a 24-week period) may be considered medically necessary in patients who do not adequately respond to every 6 week dosing.</u> o JIA, RA, and Uveitis: Maximum of 13 infusions in a 1 year period based on a <u>recommended infusion interval of up to every 4 weeks.</u> - Initial authorization shall be reviewed at 6 months. - Continuous authorization or re-authorization (after the initial 6-month period) shall be reviewed at least annually, and clinical documentation indicating that there is disease stability or improvement must be provided.
<p>Ixekizumab (Taltz)</p>	<ul style="list-style-type: none"> - Up to 160 mg initially at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12 (per manufacturer labeling), then 80 mg every 4 weeks. - Authorization may be reviewed annually to confirm that current medical necessity criteria are met and that the medication is effective.
<p>Secukinumab (Cosentyx)</p>	<ul style="list-style-type: none"> - Axial SpA, PsA, and PsO: For all patients, 150 mg initially and at weeks 1, 2, 3, and 4, then 150 mg every 4 weeks thereafter. - For PsO and PsA: Doses of up to 300 mg every 4 weeks may be considered medically necessary for patients in whom the 150 mg dose has shown benefit, but who have not achieved clinical remission after at least a 12-week trial. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
<p>Tocilizumab (Actemra) - Intravenous</p>	<p>JIA and RA:</p> <ul style="list-style-type: none"> - <u>Initial authorization:</u> Maximum of 6 infusions in a 6 month period. - <u>Continued authorization:</u> Maximum of 13 infusions in a 1 year period based on a recommended infusion interval of every 4 weeks. <p>SJIA:</p> <ul style="list-style-type: none"> - <u>Initial authorization:</u> Maximum of 12 infusions in a 6 month period (per manufacturer labeling). - <u>Continued authorization:</u> Maximum of 13 infusions in a 1 year period based on a <u>recommended infusion interval of every 4 weeks, or 26 infusions in a 1 year period based on a recommended infusion interval of every 2 weeks.</u> <p>For all other conditions:</p> <ul style="list-style-type: none"> - Initial authorizations shall be reviewed at 6 months. - Continued authorizations or re-authorizations (after the initial period) shall be

	<p>reviewed at least annually, and clinical documentation indicating that there is disease stability or improvement must be provided.</p>								
Tocilizumab (Actemra) - Subcutaneous	<ul style="list-style-type: none"> - GCA: Maximum of 52 syringes in a 1 year period based on a recommended injection interval of once every week. - RA: Maximum of 52 syringes in a 1 year period based on a recommended injection interval of once every week or every other week. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and the medication is effective. 								
Tofacitinib (Xeljanz, Xeljanz XR)	<ul style="list-style-type: none"> - Xeljanz: Up to 60 tablets per 30 days. - Xeljanz XR: Up to 30 tablets per 30 days. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and the medication is effective. 								
Ustekinumab (Stelara)	<ul style="list-style-type: none"> - PsO and PsA: For all patients regardless of weight, 45 mg initially and at week 4, then 45 mg every 12 weeks thereafter. <ul style="list-style-type: none"> o For patients in whom the 45 mg dose has shown benefit, but who have not achieved clinical remission after at least a 12-week trial, doses of up to 90 mg every 12 weeks may be considered medically necessary. - CD: A single, weight-based IV infusion initially, then 90 mg SC every 8 weeks. Initial IV dosing is as follows: <table border="1" data-bbox="363 968 1273 1161"> <thead> <tr> <th>Weight</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>55 kg or less</td> <td>260 mg</td> </tr> <tr> <td>More than 55 kg to 85 kg</td> <td>390 mg</td> </tr> <tr> <td>More than 85 kg</td> <td>520 mg</td> </tr> </tbody> </table> <p>- Authorization shall be reviewed at least annually to confirm that current medical necessity criteria are met and the medication is effective.</p>	Weight	Dose	55 kg or less	260 mg	More than 55 kg to 85 kg	390 mg	More than 85 kg	520 mg
Weight	Dose								
55 kg or less	260 mg								
More than 55 kg to 85 kg	390 mg								
More than 85 kg	520 mg								
Vedolizumab (Entyvio)	<ul style="list-style-type: none"> - <u>Initial authorization:</u> Up to 6 infusions in a 6 month period. - <u>Continued Authorization</u> - Maximum of 7 infusions in a 1 year period based on a recommended infusion interval of every 8 weeks (per manufacturer labeling). - Initial authorization shall be reviewed at 6 months. - Continued authorization or re-authorization (after the initial 6 month period) shall be reviewed at least annually and clinical documentation indicating that there is disease stability or improvement must be provided. 								

CD: Crohn's disease, GCA: Giant Cell Arteritis, JIA: juvenile idiopathic arthritis, PSA: psoriatic arthritis, PSO: psoriatic arthritis, RA: Rheumatoid arthritis, SpA: spondyloarthritis, UC: ulcerative colitis

Table 2. Not Medically Necessary Uses

Adalimumab (Humira)	Adalimumab (Humira) is considered not medically necessary when used in maintenance doses exceeding 40 mg every 2 weeks for rheumatoid arthritis (RA).
Etanercept (Enbrel)	Etanercept (Enbrel) is considered not medically necessary when used in maintenance doses exceeding 50 mg per week.
Secukinumab (Cosentyx)	Secukinumab (Cosentyx) lyophilized powder in a vial is not considered medically necessary.

IV. Investigational uses

- A. Combination use of biologic DMARDs and non-biologic DMARDs, such as apremilast (Otezla) and tofacitinib (Xeljanz/Xeljanz XR), is considered investigational.
- B. Unless otherwise specified in section I, medications included in this policy are considered investigational when used for all other conditions, due to lack of published data, lack of high quality data, or lack of positive data, including for doses in excess of those listed in Section III, Table 1 (above). Details of select investigational uses are listed below.

Arthritis associated with IBD

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in patients with arthritis associated with IBD, including Crohn's and ulcerative colitis.
- The evidence is limited to small, short-term, open-label trials and case studies with infliximab. Given the lack of blinding and lack of control arm, the incremental benefit of infliximab therapy is uncertain.^[1]
- There are no reliable published clinical trials with any other biologics.

Ankylosing spondylitis (AS)

- There is no reliable evidence to establish the efficacy or safety of nbDMARDs and non-TNFi, with the exception of secukinumab, for the treatment of axial spondyloarthritis, including AS.
- One double-blind, placebo-controlled, single-center study evaluated the efficacy of apremilast in patients with AS. The primary endpoint, change in Bath Ankylosing Spondylitis Disease Activity Index at week 12, was not met.^[2]

Behçet's Disease

- The literature on infliximab in the treatment of Behçet's disease consists primarily of case reports and small case series, with few follow-up studies to confirm findings of preliminary reports and few randomized clinical trials. Higher quality data is needed to establish the safety and efficacy of infliximab in the treatment of Behçet's disease.^[3]
- The literature on etanercept in the treatment of Behçet's disease is limited to small, short-term trials that found with conflicting benefit compared to placebo.^[3]
- Small clinical trials, case reports and expert opinion suggest modest clinical benefits are associated with bDMARD use, however high quality evidence from, larger, well designed randomized controlled trials are needed to establish the safety and efficacy of bDMARDs in Behçet's disease.^[4]
- Apremilast is currently approved for Behçet's disease in Europe; however, there is no published data evaluating the efficacy of apremilast in patients in the U.S.
- Other available treatment options include (but are not limited to) corticosteroids, colchicine, azathioprine, cyclophosphamide, and cyclosporine. ^[3]

Blau's Syndrome (Familial Juvenile Systemic Granulomatosis)

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of Blau's syndrome.
- No randomized, controlled trials have been published evaluating the use of adalimumab in patients with Blau's syndrome.

Combination Use of Apremilast (Otezla) with bDMARDs

- There is no reliable evidence to establish the efficacy or safety of the combined use of apremilast and bDMARDs in the treatment of PsO or PsA.
- There are no randomized, controlled trials evaluating the combined use of apremilast and any bDMARD. The evidence is limited to retrospective studies in small numbers of patients. Additional studies are needed to establish long-term efficacy and the overall risk-benefit profile of combination use. [5]

Erosive/Inflammatory Osteoarthritis (OA)

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of Blau's syndrome
- A small, open-label pilot trial of adalimumab in 12 patients with erosive/inflammatory OA did not demonstrate a significant benefit as measured by ACR20 after four weeks of treatment.[6]

Giant Cell Arteritis (GCA)

- With the exception of tocilizumab, there is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of GCA.
- A randomized, placebo-controlled trial was conducted to evaluate the efficacy of infliximab in 44 patients with newly diagnosed giant-cell arteritis. At week 22, infliximab therapy did not increase the proportion of patients without relapse (primary endpoint) compared to placebo (p = 0.65). In this setting, infliximab offered no clinical benefit.[7]

Graft Versus Host Disease (GVHD)

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of GVHD.
- In one open-label clinical trial (n=62) incidences of GVHD-related mortality, non-relapse mortality, and overall survival were not different between patients treated with infliximab or placebo.[8]

Granuloma Annulare

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of granuloma annulare.
- While case reports have been published describing the treatment of granuloma annulare with etanercept, other reports have been published describing no effect, or an association with the formation of granuloma annulare and treatment with TNF-alfa inhibitors, including etanercept. Additional information is necessary to the benefit of etanercept in this population.[9]

Guttate Psoriasis

- Guttate psoriasis is a type of cutaneous psoriasis. It is characterized by the presence of

small, erythematous papules whereas plaque psoriasis is characterized itchy, red, scaly, raised lesions on the skin. Guttate psoriasis is typically managed with topical agents or UV light therapy

- There is no evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of guttate psoriasis.

Immune-mediated reactions (other than colitis) due to immunotherapy

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of immune-mediated reactions, including but not limited to pneumonitis, hepatitis, or arthritis, due to PD-1, PDL-1, or CTLA4 inhibitors.
- PD-1, PDL-1, and CTLA4 inhibitors contain warnings for immune-mediated hepatitis. In clinical trials, patients who experienced immune-mediated hepatitis were managed with systemic corticosteroids and mycophenolate.
- For immune-mediated hepatitis, NCCN guidelines state that mycophenolate is recommended instead of infliximab due to the concern for hepatotoxicity with infliximab.

Inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis)

- There is no reliable evidence to establish the efficacy or safety of abatacept, apremilast, certolizumab, etanercept, anakinra, secukinumab, or tofacitinib in the treatment of inflammatory bowel disease.
- In a review of four clinical trials evaluating the use of abatacept in the treatment of Crohn's disease and ulcerative colitis, the authors concluded that abatacept was not efficacious for these conditions.^[10]
- The efficacy of secukinumab in Crohn's disease was evaluated in a small, randomized, placebo-controlled trial in 59 patients. The study did not meet the primary endpoint of reduction of Crohn's Disease Activity Index by at least 50 points. Further studies are needed to establish the benefit of secukinumab in this population.^[11]
- There are no reliable, published studies that evaluate the efficacy or safety of golimumab (Simponi) in Crohn's disease.

Kawasaki Disease

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of Kawasaki disease.
- Infliximab has been studied in several small trials; however benefit was not consistently demonstrated. Larger randomized controlled trials are needed to establish efficacy of infliximab in this population.
 - * One small prospective trial (n=24) in patients with acute Kawasaki disease and fever evaluated infliximab versus intravenous immune globulin (IVIG). Cessation of fever occurred in 11 of 12 patients treated with infliximab and 8 of 12 patients with IVIG.^[12]
 - * A retrospective review of patients with IG-resistant Kawasaki disease who were retreated either with additional immune globulin (n = 86) or infliximab (n = 20), found that patients receiving infliximab (Remicade) had faster resolution of fever and fewer days of hospitalization.^[13]
 - * A double-blind, randomized, controlled trial evaluated the efficacy of infliximab in patients with IG-resistant Kawasaki disease. Patients received infliximab

(n=98) or placebo (n=98), added on to standard therapy. While improvement was seen in several secondary endpoints, the study failed to meet its primary endpoint of treatment resistance.^[14]

Multicentric Castleman's Disease

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of multicentric Castleman's disease.
- Evidence to support use of tocilizumab in patients with multicentric Castleman's disease is limited to small open-label trials. Randomized, controlled trials are needed to establish efficacy and safety of tocilizumab in this population.^[15]

Peripheral spondyloarthritis/spondyloarthropathy

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of peripheral spondyloarthritis.
- Evidence for the use of infliximab in spondyloarthropathy is limited to a small randomized, controlled trial in 40 patients. There was a statistically significant improvement in disease activity in patients treated with infliximab versus placebo; however, larger randomized controlled trials are needed to confirm these results.^[16]
- Despite promising results of clinical trials evaluating adalimumab in peripheral spondyloarthritis, use of adalimumab is considered investigational until high quality, long-term clinical trials confirm the efficacy and safety of adalimumab in this setting.
^[17,18]

Psoriasis

- There is no reliable evidence to establish the efficacy or safety of tocilizumab, certolizumab, anakinra, abatacept, golimumab or tofacitinib in the treatment of psoriasis.
- - A Phase 2 trial suggests that treatment with certolizumab has clinical benefit in the treatment of psoriasis; however, larger, well designed randomized-controlled trials are needed to establish the optimum safe and effective dose of certolizumab pegol in the management of psoriasis.^[19]

Psoriatic arthritis (PsA)

- There is no reliable evidence to establish the efficacy or safety of tocilizumab, certolizumab, anakinra, abatacept, or tofacitinib in the treatment of psoriatic arthritis.
- Evidence for the use of abatacept in psoriatic arthritis is limited to a small, Phase 2 trial, in which there was no difference in ACR20 response between abatacept and placebo groups. Larger randomized controlled trials are needed to establish the optimum dose, and the safety and efficacy of abatacept (Orencia) in this condition.^[20]

Pulmonary sarcoidosis

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of pulmonary sarcoidosis.
- Two clinical trials have evaluated the use of infliximab in sarcoidosis.
 - * One randomized, placebo-controlled trial in patients with extrapulmonary and pulmonary sarcoidosis reported improvements in disease severity in patients

treated with infliximab compared to placebo; however, results were not sustained in a 24-week washout period. [21]

- * One randomized, placebo-controlled trial evaluated infliximab in pulmonary sarcoidosis and found a small change the % predicted forced vital capacity compared to placebo. Though statistically significant, the clinical relevance of the numerically small change is unclear, particularly because there was no treatment benefit demonstrated in the other major secondary clinical endpoints.[22]
- * Additional data is necessary to confirm efficacy of infliximab in pulmonary sarcoidosis.
- One double-blind, randomized controlled trial in 16 patients suggest a modest benefit with adalimumab in cutaneous sarcoidosis; however, larger randomized controlled trials are needed to confirm these results. No randomized controlled trials have been published evaluating the use of adalimumab (Humira) in patients with pulmonary sarcoidosis. [23]

Pyoderma Gangrenosum

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of pyoderma gangrenosum.
- In a small randomized, placebo-controlled trial (n-29), 69% of patients treated with infliximab achieved a clinical response and (21%) achieved remission. Larger randomized controlled trials are needed to confirm these results.[24]

Reactive Arthritis/Reiter's Syndrome

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of reactive arthritis/Reiter's Syndrome.

Relapsing Polychondritis

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of relapsing polychondritis.
- Evidence supporting the use of tocilizumab in relapsing polychondritis is limited to small case series.[25,26]

Rheumatoid arthritis (RA)

- There is no reliable evidence to establish the efficacy or safety of secukinumab, vedolizumab, apremilast, or ustekinumab in the treatment of rheumatoid arthritis.
- In a Phase 2, dose-finding study of 237 patients with rheumatoid arthritis, the primary endpoint was not achieved for any secukinumab dose.[27,28]

Sacroiliitis

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of sacroiliitis.
- A small randomized controlled study reported a modest benefit with infliximab in patients with early sacroiliitis, as determined by magnetic-resonance imaging. Larger randomized controlled trials are needed to confirm these results.[29]

Sciatica

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of sciatica.
- Evidence for infliximab in the treatment of sciatica is limited to a randomized controlled trial in 40 patients. At 52 weeks, 67% of patients who received infliximab (Remicade) reported no pain compared with 63% of patients who received placebo ($p = 0.72$). This difference was not statistically significant.^[30,31]
- There are no randomized controlled trials that evaluate the efficacy and safety of a commercially available formulation of etanercept in the treatment of sciatica.
- Evidence for adalimumab in the treatment of sciatica is limited to a small randomized, controlled trial evaluated adalimumab in 61 patients. There was a modest improvement in pain as measured by a 10-point visual analog scale and at three years, the need for back surgery was reduced in adalimumab-treated patients; however, larger clinical trials are needed to confirm the benefit of adalimumab in this population.^[32,33]

Scleroderma

- There is insufficient evidence to support the use of tocilizumab for scleroderma. The evidence is limited to one small, placebo-controlled, phase 2 trial using subcutaneous tocilizumab (n=88). The trial found a change in modified Rodan skin score, but no significant difference in skin thickening, disability, fatigue, itching, or patient or clinician global disease severity. Larger Phase 3 trials are needed to establish the safety and efficacy of tocilizumab for scleroderma. ^[34]

Sjögren's Syndrome

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of Sjögren's syndrome.
- Evidence for etanercept in Sjögren's syndrome is limited to a small trial, in which there were no significant differences in the subjective measures of disease severity. ^[35]
- Evidence for anakinra is limited to a placebo-controlled trial in which patients with Sjögren's syndrome failed to find a statistically-significant improvement in fatigue as measured by a visual analog scale in patient receiving anakinra compared with placebo. An ad-hoc analysis found suggestions of a clinically relevant effect, but larger, well designed trials are needed to establish safety and efficacy for Sjögren's syndrome.^[36]

Systemic Lupus Erythematosus (SLE)

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of SLE.
- A small uncontrolled clinical trial reported modest efficacy with infliximab in patients with systemic lupus erythematosus, though larger, better designed trials are needed to confirm these results.^[37]
- A small preliminary study assessing the use of tocilizumab in patients with SLE found promising signs of response, but larger, controlled studies will be needed to establish the efficacy and safety in this population.^[38]
- One small randomized, placebo-controlled trial evaluated the use of abatacept in patients with non-life-threatening SLE and polyarthritis. The primary endpoint (proportion of patients with a new flare of SLE) was not met, but was suggestive of a

positive effect in certain exploratory measures. Further study is needed to establish the safety and efficacy of abatacept in SLE.^[39]

Uveitis

- With the exceptions of adalimumab and infliximab, there is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of uveitis.
- Efficacy of secukinumab in non-infectious uveitis was evaluated in three, Phase 3 studies, which found no statistically significant differences in uveitis recurrence between secukinumab and placebo groups in any study. The dosing regimens varied by study.^[40]

Vedolizumab – Every 4 Week Dosing

- There is insufficient evidence to support superiority of every 4 week dosing compared to every 8 week dosing of Entyvio. Although vedolizumab was studied at every 4 weeks in phase 3 trials it was not shown to be more effective than every 8 week dosing. Dose intensification from every 8 weeks to every 4 weeks has also not been studied. Additional studies are needed to identify if there is additional benefit with more frequent administration.^[41-43]
- Additionally, there is no evidence that higher or more frequent doses of vedolizumab (Entyvio) are more effective or safer in patients who are refractory to every 8 week dosing.^[41-43]

Wegener's Granulomatosis

- There is no reliable evidence to establish the efficacy or safety of bDMARDs or nbDMARDs in the treatment of Wegener's Granulomatosis.
- Evidence for infliximab is limited to one small clinical trial in 17 patients. Both infliximab and rituximab appeared to provide benefit in achieving complete or partial response; however, there was a trend favoring rituximab. Additionally, rituximab was better able to maintain remission during the long-term follow-up.^[44]

Position Statement

- There are many treatments for chronic inflammatory conditions that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- Non-medical therapies, such as prescribed exercise therapy, physical therapy, weight loss, and smoking cessation are important treatment plan components for patients suffering from many chronic inflammatory conditions.
- When a systemic medication therapy is needed to manage a chronic inflammatory condition, generic oral therapies usually offer the best value.
- When non-medical therapies and oral medications are inadequate, a biologic medication may be appropriate.
- Preferred/formulary biologic medications for the treatment of chronic inflammatory conditions include: adalimumab (Humira), certolizumab (Cimzia), infliximab (Remicade), golimumab SC (Simponi), golimumab IV (Simponi Aria), and ustekinumab (Stelara).
- Infliximab-abda (Renflexis) and infliximab-dyyb (Inflectra) are biosimilars to infliximab (Remicade). While they share most indications with infliximab (Remicade), they are not the preferred formulation of infliximab.

Few studies have shown that any one biologic medication is more effective than another in the treatment of chronic inflammatory conditions.- When there is no demonstrated difference in safety or efficacy, the medication with the lowest cost often provides the best value for members.

- Individual responses and tolerability of biologics are unpredictable and may vary between patients. If one biologic agent provides an inadequate response, another biologic may yet be effective.
- Due to the potential for development of antibodies with anti-TNF therapies which may result in loss of efficacy, clinical practice guidelines generally recommend a trial with one to two anti-TNF therapies. ^[45-49] For those who have an inadequate response or intolerance to two anti-TNF therapies, it is reasonable to consider a biologic with an alternative mechanism of action and proven efficacy for the patient's diagnosis.
- All DMARDs are immunosuppressants and carry a risk of increased infection or malignancy. Risk may vary by mechanism of action, though one has not been proven superior to another.
- There is significant variation in recommended dosing across indications for individual medications; therefore, when multiple dosage forms of a biologic agent are available, coverage can be provided for those indications where the dosage form has been evaluated in randomized controlled trials, the dosage form has been proven safe and effective, and for which the dosage form has an established dose. For all other indications, the specific dosage form will be considered investigational.
- Given that more than half of all patients respond to the lower doses of secukinumab (Cosentyx) or ustekinumab (Stelara) for PsO (150 mg and 45 mg, respectively), and the significant cost difference between the lower and higher doses, a trial of 150 mg of secukinumab (Cosentyx) or 45 mg of ustekinumab (Stelara) represents the best treatment value. When treatment with the lower dose has resulted in some, yet

inadequate, benefit, a continuation of treatment with the higher FDA-approved dose is deemed appropriate.

- Subcutaneous abatacept (Orencia) does not require an IV loading dose when used for JIA or adult PsA.
- Clinical practice guidelines for the treatment of UC indicate that for patients who initially respond to infliximab (Remicade) and begin to lose response, an increase in dose or shortening of the interval between infusions may improve the likelihood of successful treatment. These guidelines acknowledge that these strategies have not been evaluated in a controlled manner.

Evidence summary:

Rheumatic Conditions – Background

- Treatments for rheumatic conditions may include non-medical therapies, medications for the management of symptoms, medications that modify the disease course such as oral or biologic and non-biologic disease modifying anti-rheumatic drugs (bDMARDs and nbDMARDs).
- Medications to control inflammation such as nonsteroidal antiinflammatory medications (e.g. ibuprofen, indomethacin, and naproxen) and glucocorticoids (oral or injected into the joint) are effective for the management of symptoms, particularly during the early stages of disease.
- Generic, conventional DMARDs (cDMARDs), including methotrexate (MTX), hydroxychloroquine, leflunomide, and sulfasalazine are effective for decreasing symptoms and slowing disease progression, have a proven track record, and have been the standard of care for many years.
 - * MTX is considered effective in the treatment of rheumatoid arthritis (RA) and is the standard reference DMARD to which newer bDMARDs and nbDMARDs are compared for efficacy.
 - * Generic oral therapies have known potential risks. The management of these risks is well established.
- bDMARDs can also decrease symptoms, help preserve joint functioning, and slow the progression of chronic inflammatory conditions; however, these medications also have significant risks.
- There is no comparative safety data within the biologics class that indicates one medication or mechanism of action is safer than alternatives, including bDMARDs compared to nbDMARDs.
- In RA, the best response is seen when MTX is used concomitantly with any of the biologics. Infliximab (Remicade) and golimumab (Simponi, Simponi Aria) have been shown to be effective only when used with MTX.
- Provider-administered products are covered under the medical benefit and self-administered products are covered under the pharmacy benefit.

Rheumatic Conditions – Axial Spondyloarthritis (SpA)

- Several bDMARDs have been shown to be effective in the treatment of AS including the following:
 - * Adalimumab (Humira)
 - * Certolizumab pegol (Cimzia)
 - * Etanercept (Enbrel)
 - * Golimumab (Simponi)
 - * Infliximab (Inflectra)
 - * Infliximab (Remicade)
 - * Secukinumab (Cosentyx)
- All of these agents, with the exception of certolizumab pegol (Cimzia), have high quality data in the treatment of AS (see Table 3) and, therefore, can be indirectly compared based on their calculated NNTs (see Table 4).
- With the exception of certolizumab pegol (Cimzia), the efficacy of these agents in the treatment of AS is similar.
- Secukinumab (Cosentyx) has a novel mechanism of action and has the least amount of market experience. Long-term safety has not been established.
- There is moderate quality evidence to support the use of bDMARDs, particularly TNFi, in non-radiographic axial SpA. Clinical trials have consistently shown that treatment with TNFi reduced disease activity in this population.

Rheumatic Conditions – Juvenile Idiopathic Arthritis (JIA); Juvenile Rheumatoid Arthritis (JRA)

- Several bDMARDs have been shown to be effective in the treatment of JIA including:
 - * Abatacept (Orencia) intravenous
 - * Adalimumab (Humira)
 - * Etanercept (Enbrel)
 - * Tocilizumab (Actemra) intravenous
- Due to lack of high quality data, the comparative efficacy for these agents in the treatment of JIA is uncertain.

Rheumatic Conditions – Psoriatic Arthritis (PsA)

- Several bDMARDs and nbDMARDs have been shown to be effective in the treatment of PsA including the following:
 - * Adalimumab (Humira)
 - * Apremilast (Otezla)
 - * Certolizumab pegol (Cimzia)
 - * Etanercept (Enbrel)
 - * Golimumab (Simponi)
 - * Infliximab (Remicade)

- * Secukinumab (Cosentyx)
- * Ustekinumab (Stelara)
- All of these agents, with the exception of certolizumab pegol (Cimzia) and secukinumab (Cosentyx) have high quality data in the treatment of PsA (see Table 3) and, therefore, can be indirectly compared based on their calculated NNTs (see Table 4).
- With the exception of certolizumab pegol (Cimzia) and secukinumab (Cosentyx), the efficacy of these agents in the treatment of PsA is similar.
- The efficacy of apremilast (Otezla) cannot be determined with precision, although it appears to be less effective in patients naïve to bDMARD treatment [NNT to achieve ACR20=7 for bDMARD-naïve patients and NNT=4-8 for treatment experienced patients].

Rheumatic Conditions – Rheumatoid Arthritis (RA)

- Several bDMARDs and nbDMARDs have been shown to be effective in the treatment of RA including the following:
 - * Abatacept (Orencia) intravenous and subcutaneous
 - * Adalimumab (Humira)
 - * Anakinra (Kineret)
 - * Etanercept (Enbrel)
 - * Certolizumab pegol (Cimzia)
 - * Golimumab (Simponi, Simponi Aria)
 - * Infliximab (Remicade)
 - * Infliximab-abda (Renflexis)
 - * Infliximab-dyyb (Inflectra)
 - * Rituximab (Rituxan)
 - * Sarilumab (Kevzara)
 - * Tocilizumab (Actemra) intravenous and subcutaneous
 - * Tofacitinib (Xeljanz, Xeljanz XR)

Rheumatic Conditions – Systemic Juvenile Idiopathic Arthritis (SJIA)

- Several bDMARDs have been shown to be effective or are recommended by clinical practice guidelines in the treatment of SJIA including: ^[46]
 - * Abatacept (Orencia) intravenous and subcutaneous
 - * Anakinra (Kineret)
 - * Canakinumab (Ilaris)
 - * Tocilizumab (Actemra) intravenous
- Due to lack of high quality data, the comparative efficacy for these agents in the treatment of SJIA is uncertain.

Rheumatic Conditions – Giant Cell Arteritis (GCA)

- Data evaluating the use of biologic agents in the treatment of GCA is limited; however, there are few treatment options for this condition, which can result in serious complications.

- Intravenous tocilizumab (Actemra) showed benefit in a randomized controlled trial in patients with newly diagnosed or relapsing GCA (n=30). Tocilizumab (Actemra) was compared to placebo, and both groups received orally administered glucocorticoids.^[50]
 - * After 12 weeks of treatment, more patients receiving tocilizumab (Actemra) achieved remission (85%) compared to those in the placebo group (40%). Additional tocilizumab-treated patients experienced a higher frequency of relapse-free survival and lower cumulative doses of glucocorticoids after 52 weeks.
- Evidence for the use of TNFi is lacking, as several small trials have shown benefit in the treatment of GCA.

Skin Conditions – Background

- There are many treatments for psoriasis that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- Light therapy, including UVB and PUVA, is effective and safe, and PUVA may result in long-term remission. When patients are not able to receive office-administered light therapy, light units for home use may be an appropriate alternative (see Appendix 1 for absolute and relative contraindications for phototherapy/chemotherapy).
- When systemic therapy is needed to manage psoriasis, cDMARDs often provide the best value.
 - * Oral medications, including MTX, cyclosporine, and acitretin (Soriatane), have a proven track record and have been the standard of care for many years.
 - * Oral medications are effective for most patients, and cyclosporine is known to work rapidly.
 - * Oral medications have known potential risks. The management of these risks is well established.
- When oral medications and phototherapy are inadequate, a biologic agent may be appropriate for patients with a significant amount of psoriasis (e.g. at least 10% BSA); however, these medications also have significant risks.
- Evidence-based guidelines for hidradenitis suppurativa are not available, primarily due to lack of data. Patients may benefit from non-pharmacologic interventions such as good personal hygiene, smoking cessation and weight-loss. When systemic therapy is needed to manage hidradenitis suppurativa, oral therapies often provide the best value.^[51]
 - * Topical clindamycin and tetracyclines have a proven track record of safety and have been the standard of care for mild to moderate hidradenitis suppurativa.

Skin Conditions – Chronic Plaque Psoriasis (PsO)

- Several bDMARDs have been shown to be effective in the treatment of PsO including the following:
 - * Adalimumab (Humira)
 - * Adalimumab-atto (Amjevita)

- * Brodalumab (Siliq)
- * Etanercept (Enbrel)
- * Etanercept-szszs (Erelzi)
- * Infliximab (Remicade)
- * Infliximab-dyyb (Inflectra)
- * Ixekizumab (Taltz)
- * Secukinumab (Cosentyx)
- * Ustekinumab (Stelara)
- All of these agents have high quality data in the treatment of PsO (see Table 3) and, therefore, can be indirectly compared based on their calculated NNTs (see Table 4).
- Given that more than half of all patients respond to the lower doses of secukinumab (Cosentyx) for PsO, and the significant cost difference between the lower and higher doses, a trial of 150 mg of secukinumab (Cosentyx) represents the best treatment value.
 - * Two randomized, controlled trials evaluated two doses (150 mg and 300 mg) of secukinumab (Cosentyx) versus placebo in patients with moderate to severe PsO. One trial included etanercept (Enbrel) as an active comparator. The co-primary endpoints included the Psoriasis Area Severity Index 75 (PASI75) response rate and a response of 0 or 1 on the modified Investigator's Global Assessment (IGA) at 12 weeks.^[52,53]
 - * Regardless of dose, a significantly higher proportion of patients treated with secukinumab (Cosentyx) achieved the primary endpoint compared to placebo, in both trials. After 12 weeks, PASI75 scores ranged from 67%-71% and 76%-82% for the 150 mg and 300 mg doses, respectively. Peak response rates were observed after 16 weeks of treatment.
 - * When treatment with 150 mg has resulted in some benefit after 12 weeks, but has not achieved PASI75, a continuation of treatment with 300 mg may be appropriate.

Hidradenitis Suppurativa

- High quality data evaluating the use of bDMARDs in the treatment of hidradenitis suppurativa (HS) is not available; however, there are few treatment options for this condition.
- Although adalimumab (Humira) is FDA approved for the treatment of HS, infliximab (Remicade) also has data to support use in this indication.^[51]
 - * A high quality systematic review showed that weekly-dosed adalimumab (Humira) improved quality of life in HS compared to placebo; although, the effect size was approximately equal to what is considered a minimally clinically important difference.
 - * In the same systematic review, infliximab (Remicade) also improved quality of life compared to placebo, with an effect size well above the threshold for a minimally clinically important difference.
- Pooled data from two unpublished trials show that adalimumab (Humira) significantly improved the hidradenitis suppurativa response rate after 12 weeks of treatment;

however, the studies were graded as low confidence due to lack of trial details and differences in baseline characteristics of the treatment groups. Efficacy and safety beyond 12-weeks of treatment has not been established.^[54]

- More randomized controlled trials are needed to understand relative efficacy of bDMARDs, the safety associated with weekly-dosed adalimumab (Humira) and role of oral, non-biologic treatments for HS.

Gastrointestinal conditions – Background

- There are many treatments for Crohn’s disease (CD) and ulcerative colitis (UC) that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- Lifestyle interventions, such as smoking cessation and diet modification, are important components of a comprehensive treatment plan for patients suffering from CD.
- When medication therapy is needed to manage CD and UC, oral and topical (administered rectally) therapies often provide the best value.
 - * First-line therapies to induce remission include:
 - Patients with CD: oral corticosteroids, MTX, aminosalicylates (e.g. mesalamine, balsalazide, sulfasalazine), azathioprine, or mercaptopurine (6-MP).
 - Patients with UC: oral aminosalicylates (e.g. sulfasalazine), topical mesalamine or corticosteroids (e.g. budesonide), or oral corticosteroids, depending on the extent and location of disease.
 - Due to the potential for severe adverse effects, the use of conventional corticosteroids such as prednisone is generally reserved for patients with moderate-to-severe disease who failed to respond to first-line therapies. Use is generally limited in duration and frequency.
 - Corticosteroids such as prednisone are effective in patients with both CD UC. Dosages in the range of 40 mg – 60 mg/day or 1 mg/kg/day of prednisone or equivalent are effective for induction of remission. ^[49-51]
 - * First-line therapies to maintain remission include:
 - Patients with CD: MTX and azathioprine.
 - Patients with UC: oral aminosalicylates (e.g. sulfasalazine), topical mesalamine or corticosteroids, or oral corticosteroids, depending on the extent and location of disease.
- When non-medical therapies and oral/topical medications are inadequate, a bDMARD may be appropriate for induction and/or maintenance of disease remission.

Gastrointestinal conditions – Crohn’s Disease (CD)

- Several biologic agents have been shown to be effective in the treatment of CD including the following:
 - * Adalimumab (Humira)

- * Certolizumab pegol (Cimzia)
- * Infliximab (Remicade)
- * Natalizumab (Tysabri)
- * Vedolizumab (Entyvio)
- * Ustekinumab (Stelara)
- Adalimumab (Humira), infliximab (Remicade), and ustekinumab (Stelara) have demonstrated efficacy for the induction and maintenance of remission of CD (see Table 3).
- Due to the risk of serious (sometimes fatal) adverse events with natalizumab (Tysabri), it is recommended that it only be used after other treatment options have failed.
- Due to lack of head-to-head studies in CD, the comparative efficacy for these agents is uncertain.
- There are no controlled trials that evaluate the use of golimumab (Simponi or Simponi Aria) in CD.

Gastrointestinal conditions – Immune-mediated Colitis

Serious or steroid-refractory colitis is a known adverse event associated with checkpoint inhibitors such as ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda).

Gastrointestinal conditions – Ulcerative Colitis (UC)

- Several biologic agents have been shown to be effective in the treatment of UC including the following:
 - * Adalimumab (Humira)
 - * Golimumab (Simponi)
 - * Infliximab (Remicade)
 - * Vedolizumab (Entyvio)
- Due to a lack of head-to-head comparative studies, the overall comparative efficacy for these agents in the treatment of UC is uncertain.
- There are no controlled trials that evaluate the use of certolizumab (Cimzia) or natalizumab (Tysabri) in ulcerative colitis.

Uveitis

- Data evaluating the use of biologic agents in the treatment of uveitis is limited; however, there are few treatment options for this condition.
- Adalimumab (Humira) was compared to infliximab (Remicade) in an open-label prospective, comparative, multicenter cohort study of childhood noninfectious chronic uveitis. [55]
 - * Thirty-three patients (22 females, 11 males, median age 9.17 years) with refractory, vision-threatening, noninfectious active uveitis were enrolled, and

received for at least 1 year, infliximab (Remicade) at a dose of 5 mg/kg at weeks 0, 2, and 6, and then every 6 to 8 weeks, or adalimumab (Humira) at a dose of 24 mg/m² every 2 weeks.

- * There was no demonstrable difference between treatment groups in time to achieve remission and time to steroid discontinuation. However, at 40 months of followup, 9 (60%) of 15 children receiving adalimumab (Humira) compared to 3 (18.8%) of 16 children receiving infliximab (Remicade) were still in remission on therapy (p < 0.02).
- A published, prospective case series examined the efficacy of adalimumab (Humira) in 131 patients with refractory uveitis, and intolerance or failure to respond to prednisone and at least one other systemic immunosuppressive drug. [56]
 - * The most common cause of uveitis included JIA in 39 patients (29.7%), pars planitis in 16 patients (12.2%), and Behçet disease in 13 patients (9.9%). Twenty-seven patients (20.6%) were classified as having idiopathic forms of uveitis.
 - * For adults, adalimumab (Humira) was administered at a dose of 40 mg subcutaneously every other week. For children between ages 4 and 12 years with JIA, the recommended dose is 24 mg/m² body surface area up to a maximum single dose of 40 mg subcutaneously every other week.
 - * At the end of the six month study period, anterior chamber and posterior chamber inflammation were statistically significantly improved by 1.26 points and 0.89 points respectively (measured on the Standardization of Uveitis Nomenclature Working Group grading scheme.).
 - * Adverse events reported during the study period included injection site reactions, fatigue, hypertension, herpes zoster, infectious mononucleosis, and reactivation of chronic hepatitis C virus infection. Treatments were not discontinued for these reactions.

Cryopyrin-Associated Periodic Syndromes (CAPS)/Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

- CAPS are a group of rare genetic diseases affecting approximately 200 to 300 people in the United States and are attributed to a specific genetic mutation. [57]
- Three types of CAPS affect the majority of patients: [57]
 - * Neonatal-Onset Multisystem Inflammatory Disease (NOMID) – Urticaria-like rash, CNS involvement [papilledema, cerebrospinal fluid (CSF) pleocytosis, or sensorineural hearing loss], elevated C-reactive protein (CRP), or epiphyseal and/or patellar overgrowth on radiographs.
 - * Familial Cold Auto-Inflammatory Syndrome (FCAS) – Recurrent intermittent episodes of fever and rash that primarily followed natural, artificial (e.g. air conditioning), or both types of generalized cold exposure.
 - * Muckle-Wells Syndrome (MWS) – Syndrome of chronic fever and rash that may wax and wane in intensity and is sometimes exacerbated by generalized cold exposure. This syndrome may be associated with deafness or amyloidosis.

- Medications that affect interleukin-1 (IL-1) may be helpful in controlling the symptoms of CAPS. ^[57]
 - * Medications that affect IL-1 include anakinra (Kineret), rilonacept (Arcalyst, and canakinumab (Ilaris), all of which have FDA marketing approval for one of more forms of CAPS. ^[58-60]
 - * Due to the rarity of these conditions, it is difficult to conduct high quality scientific studies.
- There have been no head-to-head trials comparing the efficacy of anakinra (Kineret), rilonacept (Arcalyst), or canakinumab (Ilaris) against each other or any other medication in the management of CAPS.
- The efficacy of anakinra (Kineret) was evaluated in a prospective, long-term, open-label and uncontrolled study in 43 patients with NOMID aged 0.7 to 46 years who were treated for up to 60 months. ^[58,61]
 - * Treatment with anakinra (Kineret) resulted in improvements in all individual disease symptoms measured by a disease-specific Diary Symptom Sum Score (DSSS), as well as in the serum markers of inflammation.
 - * For 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of anakinra (Kineret) therapy.

Table 3. Summary of FDA Indications for Targeted Disease Modifying Anti-Rheumatic Drugs

Mechanism of action	Medication	Route	RA	PsA	AS	JIA	SJIA	CPP	HS	CD	UC	Uveitis
TNF inhibitors	Infliximab (Remicade)	IV	✓	✓	✓	✓		✓		✓ ^a	✓	
	Infliximab-abda (Renflexis)	IV	✓	✓	✓	✓		✓		✓ ^a	✓	
	Infliximab-dyyb (Inflectra)	IV	✓	✓	✓	✓		✓		✓ ^a	✓	
	Etanercept (Enbrel)	SC	✓	✓	✓	✓		✓				
	Etanercept-szsz (Erelzi)	SC	✓	✓	✓	✓		✓				
	Adalimumab (Humira)	SC	✓	✓	✓	✓		✓	✓	✓	✓	✓
	Adalimumab-atto (Amjevita)	SC	✓	✓	✓	✓		✓		✓	✓	
	Certolizumab pegol (Cimzia)	SC	✓	✓	✓					✓		
	Golimumab (Simponi)	SC	✓	✓	✓							✓
Golimumab (Simponi Aria)	IV	✓										
B-lymphocyte depleter	Rituximab (Rituxan)	IV	✓									
IL-1	Anakinra (Kineret)	SC	✓				*					
IL-1β RA	Canakinumab (Ilaris)	SC					✓					
IL-6 RA	Sarilumab (Kevzara)	SC	✓									
	Tocilizumab (Actemra)	IV	✓			✓	✓					
	Tocilizumab (Actemra)	SC	✓									
IL-12, -23 RA	Ustekinumab (Stelara)	SC		✓				✓		✓ ^b		
IL-23 Blocker	Guselkumab (Tremfya)	SC						✓				
Integrin inhibitors	Natalizumab (Tysabri)	IV								✓		
	Vedolizumab (Entyvio)	IV								✓	✓	
T-lymphocyte inhibitor	Abatacept (Orencia)	IV, SC	✓	✓		✓	*					
JAK inhibitor	Tofacitinib (Xeljanz, Xeljanz XR)	PO	✓									
PDE-4 inhibitor	Apremilast (Otezla)	PO		✓				✓				
IL-17A antagonists and receptor antagonists	Brodalumab (Siliq)	SC						✓				
	Ixekizumab (Taltz)	SC						✓				
	Secukinumab (Cosentyx)	SC		✓	✓			✓				

✓ = FDA-approved indication; * = not FDA-approved, but recommended by clinical practice guidelines

^a For pediatric UC, FDA-approved and evidence is only with infliximab (Remicade). Infliximab-dyyb (Inflectra) is not indicated for pediatric UC

^b Requires an IV loading dose

Appendix 1: Absolute and Relative Contraindications for Phototherapy/Photochemotherapy

-	Type 1 or type 2 skin
-	History of photosensitivity
-	Increased risk of photosensitivity due to concomitant disease state (e.g. porphyria, systemic lupus erythematosus) or chronic medication use (e.g. tetracycline or sulfonamide antibiotics)
-	Treatment of facial or scalp lesions
-	Treatment of lesions in the groin area
-	Treatment of lesions on the palms of the hands or soles of the feet, or on nail beds
-	Presence of premalignant lesions (e.g. actinic keratosis)
-	History of melanoma or squamous-cell carcinoma
-	Physical inability to stand for the required exposure time

Appendix 2: Select List of Disease Modifying Anti-rheumatic Drugs (DMARD)

Conventional DMARDS for Rheumatic and Skin Conditions and Uveitis

azathioprine (Imuran)	methotrexate (oral, injectable)*
cyclosporine (Gengraf, Neoral, Sandimmune)*	mycophenolate (CellCept, Myfortic)
hydroxychloroquine (Plaquenil)	sulfasalazine (Azulfidine)
leflunomide (Arava)	acitretin (soriatane)*

Conventional DMARDs for Gastrointestinal conditions

azathioprine (Imuran)	mercaptopurine (6-MP; Purinethol)
balsalazide (Colazal, Giazol)	mesalamine (Apriso, Asacol HD, Delzicol, Lialda, Pentasa)
cyclosporine (Gengraf, Neoral, Sandimmune)	sulfasalazine (Azulfidine)

*: Medications used in the treatment of dermatologic conditions

Appendix 3: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Rheumatoid Arthritis (RA) [62,63]

Diagnosis of RA requires the presence of at least 4 of 7 criteria below:

1.	Morning stiffness in and around joints lasting more than 1 hour.
2.	Arthritis in at least 1 area in a wrist or proximal interphalangeal (PIP) joint (hands or fingers) for > 6 weeks.
3.	Simultaneous swelling or fluid accumulation in 3 or more joints for > 6 weeks.
4.	Symmetric (bilateral joint) involvement for > 6 weeks.
5.	Presence of rheumatoid nodules.
6.	Positive serum rheumatoid factor.
7.	Radiographic changes typical of RA (erosion or unequivocal bony decalcification in or adjacent to the involved joint) on hand and wrist present.

Appendix 4: American College of Rheumatology (ACR) Assessment Components for Improvement in Rheumatoid Arthritis (RA) [64]

-	Tender joint count.
-	Swollen joint count.
-	Patient's assessment of pain.
-	Patient's global assessment of disease activity.
-	Physician's global assessment of disease activity.
-	Patient's assessment of physical function.
-	Acute phase reactant measures (erythrocyte sedimentation rate or C-reactive protein levels.)

Appendix 5: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Giant Cell Arteritis (GCA)

Diagnosis of GCA requires the presence of at least 3 of 5 criteria below:

1.	Patient age 50 years or older
2.	New onset of localized headache
3.	Temporal artery tenderness or decreased temporal artery pulse
4.	Erythrocyte sedimentation rate of 50 mm per hour or greater
5.	Abnormal temporal artery biopsy

Glucocorticoid equivalent doses

Prednisone 40 to 60 mg
Hydrocortisone 160 to 240 mg
Cortisone 200mg to 300 mg
Prednisolone 40 to 60 mg
Methylprednisolone 32 mg to 48 mg
Dexamethasone 6 mg to 9 mg

Codes	Number	Description
CPT	96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
	96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure) (Use 96366 in conjunction with 96365, 96367)
	96367	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion, up to 1 hour (List separately in addition to code for primary procedure) (Use 96367 in conjunction with 96365, 96374, 96409, 96413 if provided as a secondary or subsequent service after a different initial service is administered through the same IV access. Report 96367 only once per sequential infusion of same infusate mix)
	96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure) (Use 96368 in conjunction with 96365, 96366, 96413, 96415, 96416. Report 96368 only once per encounter)
HCPCS	J0129	Injection, abatacept, 10 mg, for intravenous use
	J0135	Injection, adalimumab, 20 mg (to be used only when drug is given under direct supervision of a physician)
	J0717	Injection, certolizumab pegol, 1 mg (to be used only when drug is given under direct supervision of a physician)
	J1438	Injection, etanercept, 25 mg and 50 mg (to be used only when drug is given under direct supervision of a physician)
	J1602	Injection, golimumab, 1 mg, for intravenous use
	J1745	Injection, infliximab, 10 mg
	J2323	Injection, natalizumab, 1 mg
	J3262	Injection, tocilizumab, 1 mg, for intravenous use
	J3357	Injection, ustekinumab, 1 mg
	J9310	Injection, rituximab, 100 mg

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Revision History

Revision Date	Revision Summary
8/11/2017	<ul style="list-style-type: none"> - Added coverage criteria for sarilumab (Kevzara), as a non-preferred self-administered option for RA. - Added coverage criteria for subcutaneous tocilizumab (Actemra) for GCA. - Added coverage criteria for abatacept (Orencia) for PsA and updated JIA coverage criteria to include SC dosing. - Added coverage criteria for guselkumab (Tremfya), as a non-preferred self-administered option for PsO. - Added infliximab-abda (Renflexis) to policy - UC: revised step therapy requirements for vedolizumab (Entyvio)
5/12/2017	<ul style="list-style-type: none"> - Added coverage criteria for brodalumab (Siliq), as a non-preferred self-administered option for PsO - Clarified step therapy for “self-administered UC treatments.” - Updated dose and quantity limits for ixekizumab (Taltz) and secukinumab (Cosentyx) - Added the following as an investigational uses: <ul style="list-style-type: none"> o Scleroderma (any branded medication) o Use of apremilast (Otezla) in combination with targeted immunomodulators for any indication
12/16/2016	<ul style="list-style-type: none"> - Updated preferred and non-preferred products for all indications - Added infliximab-dyyb (Inflectra) to policy

Revision Date	Revision Summary
	<ul style="list-style-type: none"> - Updated investigational uses - CD: Added ustekinumab (Stelara) and revised quantity limits for infliximab - UC: Revised quantity limits for infliximab
4/8/2016	<ul style="list-style-type: none"> - AS: added secukinumab (Cosentyx), changed to diagnosis to axial SpA - PsO: added ixekizumab (Taltz), updated step therapy requirements nonpreferred drugs - Added criteria for Giant Cell Arteritis and Hidradenitis Suppurativa - PsA: Updated step therapy requirements for non-preferred drugs, added secukinumab - Updated language for combination use with an oral DMARD for infliximab and golimumab (IV) - Added Xeljanz XR to policy - Updated investigational uses
1/8/2016	Updated formatting of biologics policies, consolidating into a single policy for chronic inflammatory diseases