# Biologic Immunomodulators Prior Authorization with Quantity Limit with Preferred Products Program Summary

This program applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace.

For BCBSAL, the prior authorizatoin program will only apply only to the Biologic Immunomodulators under the pharmacy benefit: Actemra subcutaneous, Cimzia subcutaneous, Cosentyx, Enbrel, Humira, Kevzara, Kineret, Olumiant, Orencia subcutaneous, Siliq, Simponi subcutaneous, Stelara subcutaneous, Taltz, Tremfya, Xeljanz, and Xeljanz XR. These agents are also subject to a quantity limit.

## Biologic Immunomodulators Prior Authorization with Quantity Limit – with Preferred Products

### OBJECTIVE

The intent of the Biologic Immunomodulators Prior Authorization with Quantity Limit criteria is to ensure that patients prescribed therapy are properly selected according to Food and Drug Administration (FDA)-approved product labeling and/or clinical guidelines and/or clinical trials. The criteria will encourage the use of first-line conventional agents, some of which are available as generics (for example, first-line agents for arthritis indications, methotrexate and leflunomide, are both available as generics). Criteria will also encourage use of preferred biologic immunomodulators when clinically appropriate before the nonpreferred agents with appropriate dosing. This program allows continuation of therapy when patients have been receiving and are stabilized on a biologic immunomodulator.

### TARGET DRUGS

**Preferred and Nonpreferred Biologic Immunomodulators**

| Disease State | Try/Fail | Preferred | Non-preferred |
|---|---|---|---|
| Rheumatoid Arthritis (RA) | Try/Fail 2 preferred agents; then must try Xeljanz (XR) prior to any other non-preferred agent (last preferred agent is still approvable prior to Xeljanz (XR)) | Enbrel, Humira, Simponi | Actemra, Cimzia, Kevzara, Kineret, Olimiant, Orencia, Xeljanz (XR) |
| Psoriatic Arthritis | Try/Fail 3 preferred agents | Enbrel, Humira, Cosentyx, Simponi, Stelara | Cimzia, Orencia, Xeljanz (XR) |
| Plaque Psoriasis | Try/Fail 3 preferred agents | Enbrel, Humira, Cosentyx, Stelara | Comzia, Siliq, Taltz, Tremfya |
| Ankylosing Spondylitis | Try/Fail 3 preferred agents | Cosentyx, Enbrel, Humira, Simponi | Cimzia |
| Crohn's Disease | Try/Fail 2 preferred agents | Humira, Stelara | Cimzia |
| Ulcerative Colitis | Try/Fail 2 preferred agents | Humira, Simponi | Xeljanz |

| | | | |
|---|---|---|---|
| PJIA | Try/Fail 2 preferred agents | Enbrel, Humira | Orencia |
| HS | Try/Fail 1 preferred agent | Humira | N/A |
| Uveitis | Try/Fail 1 preferred agent | Humira | N/A |
| SJIA, CAPS/NOMID, CRS | N/A | N/A | N/A |

**QUANTITY LIMITS FOR TARGET DRUGS**

| Brand (generic) | GPI | Quantity Limit | Multisource Code |
|---|---|---|---|
| **Actemra® (tocilizumab)** | | | |
| 162 mg/0.9 mL syringe | 6650007000E520 | 4 syringes/28 days | M, N, O, or Y |
| **Cimzia® (certolizumab)** | | | |
| 2 x 200 mg vial, kit | 52505020106420 | 1 kit/28 days (1 kit of 2 x 200 mg vials/28 days) | M, N, O, or Y |
| 2 x 200 mg/mL syringe, kit | 52505020106440 | 1 kit/28 days (1 kit of 2 syringes/28 days) | M, N, O, or Y |
| 6 X 200 mg/mL syringe, starter kit | 52505020106460 | 1 starter kit/180 days | M, N, O, or Y |
| **Cosentyx™ (secukinumab)** | | | |
| 150 mg/mL auto-injector | 9025057500D520 00078-0639-41 | 1 package of 2 injectors/28 days | M, N, O, or Y |
| 150 mg/mL auto-injector | 9025057500D520 00078-0639-68 | 1 injector/28 days | M, N, O, or Y |
| 150 mg/mL pre-filled syringe | 9025057500E520 00078-0639-97 | 1 syringe/28 days | M, N, O, or Y |
| 300 mg/2 mL (2 x 150 mg/mL) pre-filled syringe | 9025057500E520 00078-0639-98 | 1 package of 2 syringes/28 days | M, N, O, or Y |
| **Enbrel® (etanercept)** | | | |
| 50 mg/mL syringe | 6629003000E530 | 4 syringes/28 days | M, N, O, or Y |
| 50 mg/mL SureClick autoinjector | 6629003000D530 | 4 autoinjections/28 days | M, N, O, or Y |
| 50 mg/mL Mini injector | 6629003000E230 | 4 injectors/28 days | M, N, O, or Y |
| 25 mg/0.5 mL | 6629003000E525 | 8 syringes/28 days | M, N, O, or Y |
| 25 mg/vial, kit | 66290030002120 | 8 vials/28 days | M, N, O, or Y |
| **Humira® (adalimumab)** | | | |
| 10 mg/0.1 mL syringe | 6627001500F804 | 2 syringes/28 days | M, N, O, or Y |
| 10 mg/0.2 mL syringe | 6627001500F805 | 2 syringes/28 days | M, N, O, or Y |
| 20 mg/0.2 ml syringe | 6627001500F809 | 2 syringes/28 days | M, N, O, or Y |
| Pediatric Crohn's Disease Starter Kit 40 mg/0.8mL (Both 3 and 6 syringe pack) | 6627001500F820 | 1 kit/180 days | M, N, O, or Y |
| 20 mg/0.4 mL syringe, kit | 6627001500F810 | 2 syringes/28 days | M, N, O, or Y |
| 40 mg/0.8 mL syringe, kit | 6627001500F820 | 2 syringes/28 days | M, N, O, or Y |

| Brand (generic) | GPI | Quantity Limit | Multisource Code |
|---|---|---|---|
| 40/0.4 ml syringe | 6627001500F830 | 2 syringes/28 days | M, N, O, or Y |
| Pediatric Crohn's Disease Starter kit (80 mg/0.8 mL syringe) | 6627001500F840 | 1 kit (3 syringes)/180 days | M, N, O, or Y |
| Pediatric Crohn's Disease Starter kit (40 mg/0.4 mL and 80 mg/0.8 mL syringe) | 6627001500F880 | 1 kit (2 syringes)/180 days | M, N, O, or Y |
| 40 mg/0.8 mL pen, kit | 6627001500F420 | 2 pens/28 days | M, N, O, or Y |
| Psoriasis/Uveitis Starter kit (40 mg/0.8 mL pen) | 6627001500F420 | 1 kit (4 pens)/180 days | M, N, O, or Y |
| Crohn's Disease, Ulcerative Colitis, or Hidradenitis Starter kit (40 mg/0.8 mL pen) | 6627001500F420 | 1 kit (6 pens)/180 days | M, N, O, or Y |
| 40 mg/0.4 mL pen | 6627001500F430 | 2 pens/28 days | M, N, O, or Y |
| 80 mg/0.8 mL pen, Crohn's disease, ulcerative colitis, or hidradenitis suppurtaiva Starter kit | 6627001500F440 | 1 kit (3 pens)/180 days | M, N, O, or Y |
| 80 mg/0.8 mL and 40 mg/0.4 mL pen, Psoriasis, uveitis Starter kit | 6627001500F450 | 1 kit (3 pens)/180 days | M, N, O, or Y |
| **Kevzara (sarilumab)** | | | |
| 150 mg/1.14 mL pen | 6650006000D520 | 2 pens (2.28 mL)/28 days | M, N, O, or Y |
| 200 mg/1.14 mL pen | 6650006000D530 | 2 pens (2.28 mL)/28 days | M, N, O, or Y |
| 150 mg/1.14 mL | 6650006000E520 | 2 syringes/28 days | M, N, O, or Y |
| 200 mg/1.14 mL | 6650006000E530 | 2 syringes/28 days | M, N, O, or Y |
| **Kineret® (anakinra)** | | | |
| 100 mg syringe | 66260010****** | 30 syringes/30 days | M, N, O, or Y |
| **Olumiant (baricitinib)** | | | |
| 2 mg tablets | 66603010000320 | 1 tablet/day | M, N, O, or Y |
| **Orencia® (abatacept)** | | | |
| 50 mg/0.4 mL (subcutaneous) prefilled syringe | 6640001000E510 | 4 syringes/28 days | M, N, O, or Y |
| 87.5 mg/ 0.7 mL | 6640001000E515 | 4 syringes/28 days | M, N, O, or Y |
| 125 mg/mL (subcutaneous) pre-filled syringe | 6640001000E520 | 4 syringes/28 days | M, N, O, or Y |
| 125 mg/mL (subcutaneous) ClickJect autoinjector | 6640001000D520 | 4 autoinjectors/28 days | M, N, O, or Y |
| **Siliq™ (brodalumab)** | | | |

| Brand (generic) | GPI | Quantity Limit | Multisource Code |
|---|---|---|---|
| 210 mg/1.5 mL syringe | 9025052000E520 | 2 syringes/28 days | M, N, O, or Y |
| **Simponi® (golimumab)** | | | |
| 50 mg/0.5 mL syringe | 6627004000E520 | 1 syringe/28 days | M, N, O, or Y |
| 50 mg/0.5 mL auto-injector | 6627004000D520 | 1 syringe/28 days | M, N, O, or Y |
| 100 mg/1 mL syringe | 6627004000E540 | 1 syringe/28 days | M, N, O, or Y |
| 100 mg/1 mL auto-injector | 6627004000D540 | 1 syringe/28 days | M, N, O, or Y |
| **Stelara (ustekinumab)** | | | |
| 130 mg/26 mL (5 mg/mL) | 52504070002020 | 4 vials/180 days | M, N, O, or Y |
| 45 mg/0.5 mL syringe | 9025058500E520<br>90250585002020 | 1 syringe/84 days | M, N, O, or Y |
| 90 mg/1 mL syringe | 9025058500E540 | 1 syringe/56 days | M, N, O, or Y |
| **Taltz (ixekizumab)** | | | |
| 80 mg/mL autoinjector | 9025055400D520 | 1 syringe/28 days | M, N, O, or Y |
| 80 mg/mL prefilled syringe | 9025055400E520 | 1 syringe/28 days | M, N, O, or Y |
| **Tremfya (guselkumab)** | | | |
| 100 mg/mL prefilled syringe | 9025054200E520 | 1 mL (1 syringe)/56 days | M, N, O, or Y |
| **Xeljanz® (tofactinib)** | | | |
| 5 mg tablet | 66603065100320 | 2 tablets daily | M, N, O, or Y |
| 10 mg tablet | 66603065100330 | 2 tablets/day | M, N, O, or Y |
| **Xeljanz XR® (tofactinib extended release)** | | | |
| 11 mg tablet | 66603065107530 | 1 tablet/day | M, N, O, or Y |

**PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**
**Initial Evaluation**

1. ONE of the following:
    a. There is documentation that the patient is currently being treated with the requested agent (starting on samples is not approvable)
    **OR**
    b. The prescriber states the patient is using the requested agent (starting on samples is not approvable) AND is at risk if therapy is changed
    **OR**
    c. ALL of the following:
        i. The patient has an FDA labeled/drugdex 1 or 2a level of evidence (or otherwise accepted by client) indication for the requested agent
        **AND**
        ii. ONE of the following:
            1. The patient's medication history indicates use of another biologic immunomodulator agent OR Otezla for the same FDA labeled/drugdex 1 or 2a level of evidence (or otherwise accepted by client) indication
            **OR**
            2. The patient's diagnosis does not require a conventional agent prerequisite*
            **OR**

3. The patient's medication history indicates use of one conventional agent prerequisite
   **OR**
4. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least ONE conventional agent

**AND**

iii. ONE of the following:
   1. The patient's medication history indicates trial and failure of the required amount of preferred biologic immunomodulator agents (See Preferred Agent Table) or the patient has a documented intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to all of the required preferred agents
      **OR**
   2. The request is for a FDA labeled indication that does not require a preferred product

**AND**

iv. If Stelara 90 mg is requested, ONE of the following:
   1. The patient has a diagnosis of psoriasis AND weighs >100kg AND the patient has failed (had an inadequate response to) a trial of 45mg for at least 3 months
      **OR**
   2. The patient has a dual diagnosis of psoriasis AND psoriatic arthritis AND the patient is >100kg
      **OR**
   3. The patient has a diagnosis of Crohn's disease

**AND**

2. The patient is not currently being treated with another biologic immunomodulator agent or Otezla
   **AND**
3. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   **AND**
4. The patient has been tested for latent TB when required by the prescribing information for the requested agent AND if positive the patient has begun therapy for active TB
   **AND**
5. ONE of the following:
   a. The prescribed dosage is within the program limit (FDA approved labeled dosage)
      **OR**
   b. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

*****NOTE: Conventional agent required for diagnoses of rheumatoid arthritis, juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, uveitis, Crohn's disease, and giant cell arteritis

**Length of approval:** 12 months for all agents EXCEPT Humira (adalimumab) for ulcerative colitis (UC), Siliq for plaque psoriasis (PS), Xeljanz for UC and the agents with

indications that require loading doses for new starts. For agents that require a loading dose for a new start, the loading dose will be approved following FDA labeling and also the maintenance dose for the remainder of the 12 months. Humira for UC may be approved for 12 weeks, Siliq for PS for 16 weeks, and Xeljanz for UC may be approved for 16 weeks.

**Renewal Evaluation**

***Preferred*** and ***Nonpreferred agents*** **will be approved for renewal when the following criteria are met:**

1. The patient has been previously approved for therapy through Prime Therapeutics PA process (*please note Stelara renewal must be for the same strength as the initial approval)
   **AND**
2. The patient has shown clinical improvement (i.e. slowing of disease progression or decrease in symptom severity and/or frequency)
   **AND**
3. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   **AND**
4. The patient is not currently being treated with another biologic immunomodulator agent or Otezla
   **AND**
5. ONE of the following:
   A. The prescribed dosage is within the program set limit (FDA approved labeled dosage) **OR**
   B. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

**Length of approval:** 12 months for all agents

**FDA APPROVED INDICATIONS AND DOSAGE[1-10,30,52,57,68,72,76,83-84,87-90]**

| Agent | FDA Indication(s) [d] | Dosing and administration[ab] |
|---|---|---|
| **Actemra** (tocilizumab) | CRS (≥2 yrs), GCA, JIA [PJIA and SJIA (≥2 yrs)], RA[c*] | **RA:** 4 mg/kg, increase to 8 mg/kg if needed, every 4 weeks for IV or 162 mg SQ eow up to weekly based on clinical response and weight<br>**SJIA:** Every 2 weeks, 12 mg/kg (wt <30 kg), 8 mg/kg (wt ≥30 kg)<br>**PJIA**: 8 to 10 mg/kg every 4 weeks depending on weight<br>**GCA**: 162 mg SC once every week, in combination with a tapering course of glucocorticoids<br>**CRS:** 12 mg/kg (wt <30 kg), 8 mg/kg (wt ≥30 kg) IV up to 4 doses with interval between consecutive doses of at least 8 hours, not to exceed 800mg per infusion |
| **Cimzia** (certolizumab) | AS, CD, PS, PSA, RA | **CD:** 400 mg at day 0 and weeks 2 and 4, then 400 mg q 4 weeks<br>**RA/PSA:** 400 mg at day 0 and weeks 2 and 4, then 200 mg eow (maintenance dosing of 400 mg every 4 weeks can be considered)<br>**PSA/AS**: 400 mg at day 0 and weeks 2 and 4, then 200 mg eow or 400 mg every 4 weeks<br>**PS**: 400 mg every other week; for some patients (body weight ≤90 kg) 400 mg at day 0 and weeks 2 and 4, then 200 mg every other week can be considered |
| **Cosentyx** (secukinumab) | AS, PS, PSA | **PS/PSA with PS:** 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg.<br>**PSA/AS: with loading dose-** 150 mg SC at weeks 0,1,2,3, and 4 and every 4 weeks thereafter (can go up to 300 mg)<br>**Without loading dose:** 150 mg SC every 4 weeks |
| **Enbrel** (etanercept) | AS, JIA (≥2 yrs), PS (≥4 yrs), PSA, RA | **RA/PSA/AS:** 50 mg weekly<br>**Adult PS:** 50 mg twice weekly for 3 mos, then 50 mg weekly<br>**Pediatric PS/JIA:** 0.8 mg/kg weekly (max of 50 mg weekly) |
| **Entyvio** (vedolizumab) | CD, UC | **All:** 300 mg infused over 30 minutes at 0, 2, and 6 weeks, then every 8 weeks thereafter |
| **Humira** (adalimumab) | AS, CAPS/NOMID, CD (≥6 yrs), HS, JIA (≥2 yrs), PS, PSA, RA, UC, Uveitis° | **RA/PSA/AS:** 40 mg eow; those with RA not on methotrexate may increase to 40 mg weekly<br>**JIA:** 10kg to <15kg: 10 mg eow<br>15kg to <30kg: 20 mg eow<br>≥30kg: 40 mg eow |

| | | |
|---|---|---|
| | | **Adult CD/UC:** 160 mg on day 1, 80 mg 2 weeks later (day 15), then 40 mg eow starting day 29<br>**Pediatric CD:**<br>17kg to <40kg: 80 mg on day 1, 40 mg on day 15, then 20 mg eow starting day 29<br>≥40kg: 160 mg on day 1, 80 mg on day 15, then 40 mg eow starting on day 29<br>**PS/Uveitis:** 80 mg day 0, then 40 mg eow starting one week after the initial dose<br>**HS:** Initial dose (Day 1): 160 mg (given as four 40 mg injections on Day 1 or as two 40 mg injections per day on Days 1 and 2)<br>• Second dose two weeks later (Day 15): 80 mg (two 40 mg injections in one day)<br>• Third (Day 29) and subsequent doses: 40 mg every week. |
| **Inflectra** (infliximab-dyyb) | AS, CD (>6 yrs), PS, PSA, RA, UC | **All:** 3-10 mg/kg at weeks 0, 2, 6, then every 8 weeks<br>(AS is every 6 weeks)<br>(RA can be adjusted up to 10 mg/kg every 4 weeks) |
| **Kevzara** (sarilumab) | RA | **RA:** 200 mg SC once every 2 weeks |
| **Kineret** (anakinra) | CAPS/NOMID, RA | **RA:** 100 mg subcutaneously daily<br>**CAPS/NOMID:** 1-2 mg/kg daily. Max dose of 8 mg/kg daily. |
| **Olumiant** (baricitinib) | RA | **RA:** 2 mg per day |
| **Orencia** (abatacept) | JIA (≥6 yrs, IV; ≥2 yrs SC), PSA, RA | **Infusion:** Administer on day 0, weeks 2 and 4, then every 4 weeks<br>**Intravenous RA/PSA:**<60 kg-500 mg; 60-100 kg-750 mg; >100 kg-1000 mg<br>**Subcutaneous RA:** Infusion as a loading dose per body weight, then 125 mg SC within 1 day, then 125 mg SC weekly for adults only. If no infusion, then begin weekly SC doses<br>**Intravenous JIA** (6 years of age and older)**:** <75 kg-10 mg/kg IV; >75 kg-same as adult intravenous RA dosing noted above not to exceed 1000 mg<br>**Subcutaneous JIA** (2 years of age and older): 10-<25kg: 50 mg weekly; 25-<50kg: 87.5mg weekly; ≥50 kg: 125 mg weekly<br>**Subcutaneous PSA**: 125mg once weekly without the need for an IV loading dose |
| **Remicade** (infliximab) | AS, CD (≥6 yrs), PS, PSA, RA, UC (≥6 yrs) | **All:** 3-10 mg/kg at weeks 0, 2, 6, then every 8 weeks |

| | | |
|---|---|---|
| | | (AS is every 6 weeks)<br>(RA can be adjusted up to 10 mg/kg every 4 weeks) |
| **Renflexis** (infliximab-abda) | AS, CD (≥6 yrs), PS, PSA, RA, UC | **CD:** 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks<br>**Pediatric CD:** 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks<br>**UC:** 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks<br>**RA:** 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks<br>**AS:** 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks<br>**PS/PSA**: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks |
| **Siliq** (brodalumab) | PS | **PS:** 210 mg injected at weeks 0,1,2 followed by 210mg every 2 weeks |
| **Simponi** (golimumab) | AS, PSA, RA, UC | **RA/PSA/AS**: 50 mg once monthly<br>**UC**: 200 mg Week 0, 100 mg Week 2, then 100 mg every 4 weeks |
| **Simponi ARIA** (golimumab) | AS, PSA, RA | **AS/PSA/RA**: 2 mg/kg IV at weeks 0, 4, and every 8 weeks |
| **Stelara** (ustekinumab) | CD, PS (≥12 yrs), PSA | **PS‡ adults:** 45 to 90 mg subcutaneously at day 0, week 4, then every 12 weeks<br>≤100 kg-45 mg<br>>100 kg-90 mg<br>**PS (12-17 y.o.): <60kg:** 0.75 mg/kg; **60-100kg:** 45 mg; **>100kg:** 90 mg<br>Same as adult dosing for frequency<br>**PSA:** 45 mg at day 0, week 4, then every 12 weeks<br>**PS with PSA and >100kg**:- 90 mg at day 0, week 4, then every 12 weeks<br>**CD:** 90 mg SC 8 weeks after IV induction∞, then every 8 weeks thereafter |
| **Taltz** (ixekizumab) | PS | **PS**: 160 mg (2 X 80 mg injections) SC at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks |
| **Tremfya** (guselkumab) | PS | **PS:** 100 mg SC Week 0, Week 4, and every 8 weeks thereafter |
| **Xeljanz** (tofacitinib) | PSA, RA, UC | **ALL:** 5 mg orally twice daily (5 mg once daily in patients with moderate and severe renal impairment and moderate hepatic impairment)<br>**UC**: 10 mg orally twice daily for 8 weeks; then 5 or 10 mg twice daily. Discontinue after 16 weeks of 10mg twice daily, if adequate therapeutic benefit is not achieved |
| **Xeljanz XR** (tofacitinib extended release) | PSA, RA | **ALL:** 11 mg orally once daily |

AS=Ankylosing Spondylitis, CAPS/NOMID=Cryopyrin Associated Periodic Syndrome/Neonatal-Onset Multisystem Inflammatory Disease, CD=Crohn's Disease, CRS=Cytokine Release Syndrome, GCA=Giant Cell Arteritis, HS=Hidradenitis Suppurativa, JIA=Juvenile Idiopathic Arthritis, PJIA=Polyarticular Juvenile Idiopathic Arthritis, PS=Psoriasis, PSA=Psoriatic Arthritis, RA=Rheumatoid Arthritis, SJIA=Systemic Juvenile Idiopathic Arthritis, UC=Ulcerative Colitis

‡- Labeling for psoriasis supports efficacy in patients weighing > 100 kg at the 45 mg dose but notes greater efficacy in those patients at the 90 mg dose.

a - eow-every other week, q-every

b - Concomitant use of abatacept or anakinra with TNF antagonists has been shown to increase the risk of infection without improving efficacy. As a result, FDA labeling recommends against combination therapy of two or more biologics.

c - after trial and failure of a TNF antagonist

c* - after inadequate response to one or more DMARDs

d - If age is not specified, label indicates for "adult" patients

° - indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients

∞ - A single weight-based intravenous induction dose is as follows: ≤55 kg- 260 mg (2 vials); >55 kg to 85 kg- 390 mg (3 vials); >85 kg- 520 mg (4 vials)

## CLINICAL RATIONALE

### Rheumatoid arthritis (RA)

American College of Rheumatology guidelines (2015) support a treat-to-target approach in therapy. The guidelines categorize therapy for those with recent diagnosis (<6 months) and those with an established diagnosis (> 6 months) and the severity within these two divisions. ACR recommends methotrexate unless contraindicated to all RA patients regardless of disease duration or severity. In patients with RA <6 months with moderate-high disease activity with poor prognosis DMARD combination therapy or a TNF antagonist with or without MTX, or non-TNF with or without MTX is recommended. Those with RA > 6 months that fail DMARD monotherapy, combination DMARD use, TNF inhibitor ± MTX, non-TNF ± MTX, or tofacitinib ± MTX can be used.[65] The EULAR (2013) update, echoes the ACR suggesting MTX is the preferred 1st line conventional agent (sulfasalazine or leflunomide when MTX is inappropriate). After failure to MTX, a patient with no poor prognostic factors present should change the DMARD or initiate DMARD combination therapy prior to biologic therapy. A patient with poor prognostic factors warrants the addition of a biologic reiterating that MTX has been failed prior (unless clinically inappropriate).[64]

### Systemic onset juvenile idiopathic arthritis (SJIA)

Systemic onset juvenile idiopathic arthritis (SJIA) was formerly called Still's disease and is a subset of juvenile idiopathic arthritis (JIA) that describes patients with fever, rash, and arthritis. The American College of Rheumatology (ACR) 2013 SJIA initial therapy treatment update for active systemic features includes nonsteroidal antiinflammatory drugs (NSAIDs), systemic glucocorticoids (oral or intravenous) and Anakinra (IL-1). Many children with SJIA have refractory disease, in which agents targeting interleukins IL-1 and IL-6 are used. ACR suggests continued disease activity be managed with canakinumab (IL-1), tocilizumab (IL-6), TNF-α inhibitors, methotrexate, leflunomide or options included in initial therapy not yet utilized. Treatment suggestions/decisions are based on the patient's physician global assessment (MD global) and active joint count (AJC).[41-47,53,63]

### Psoriasis and Psoriatic Arthritis (PsA)

The American Academy of Dermatology guidelines state that 80% of psoriasis patients have limited disease involvement, typically defined <5% of body surface area, and can be effectively managed with topical agents such as corticosteroids, vitamin D analogues, tazarotene, etc. For more significant disease, biologics are utilized.[31]

Approximately 10-30% of patients with psoriasis will also have PsA. EULAR Recommendations on the management of psoriatic arthritis recommend the following[56]:

- Conventional synthetic DMARDs [(csDMARDs); i.e. MTX, sulfasalazine, leflunomide] should be considered in:

    - Early stage peripheral arthritis, particularly in those with poor prognosis (i.e. swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C reactive protein and/or clinically relevant extra-articular manifestations). MTX is preferred in those with relevant skin involvement
- After failure to at least one csDMARD, therapy with a bDMARD (usually TNF-i followed by bDMARDs targeting IL-12/23 or IL-17 if TNF-i is not appropriate) should be considered
- After failure to at least one csDMARD, where a bDMARD is not appropriate, a targeted synthetic DMARD (tsDMARD), such as a PDE4-inhibitor should be considered
- In those with active enthesitis and/or dactylitis with failure to NSAIDs/local glucocorticoids injections, a bDMARD should be considered (current practice is a TNF-i)
- Predominantly active axial disease: after failure to NSAIDs, a bDMARD should be considered (current practice is a TNF-i)
- After failure to a bDMARD, switch to another bDMARD, including switching between TNF-inhibitors

**Inflammatory Bowel Disease (IBD)- Crohn's disease (CD) and Ulcerative Colitis (UC)**
American Gastroenterological Association (AGA) 2013 Crohn's Disease guideline recommendations:[67]

- For Induction of remission in moderately severe CD:
    - Systemic corticosteroids with concomitant thiopurine (6-mercaptopurine or azathioprine) or MTX to help maintain the corticosteroid-induced remission.
    - Anti-TNF (infliximab or adalimumab) with thiopurines are recommended in those refractory to standard therapies (mesalamine, antibiotics, corticosteroids and immunomodulators).
- For Remission in moderately severe CD:
    - Steroid-induced remission: Either 1) thiopurine or MTX OR 2) Anti-TNF with or without thiopurine to maintain remission
    - Anti-TNF or Anti-TNF plus thiopurine induced remission: Anti-TNF with or without thiopurine to maintain remission

AGA 2015 Ulcerative Colitis Clinical Care Pathway recommendations:[77]

- Patients are to be stratified according to colectomy risk (low vs high)
    - Low risk:
        - Inductive therapy: oral 5ASA and/or rectal 5ASA (first line therapy in distal UC) and/or oral budesonide or prednisone and/or rectal steroids
        - Maintenance therapy: oral 5ASA and/or rectal 5ASA; taper steroid over 60 days
    - High risk, outpatient (3 options):
        - Inductive therapy: short course of steroids with initiation of thiopurine; Maintenance therapy with thiopurine and taper steroids over 60 days OR Anti-TNF ± thiopurine OR vedolizumab ± thiopurine/MTX
        - Inductive therapy: Anti-TNF ± thiopurine; Maintenance with continued anti-TNF ± thiopurine
        - Inductive therapy: vedolizumab ± immunodulator; Maintenance with continued vedolizumab ± immunomodulator
    - High risk, inpatient (3 options):
        - Induction therapy: IV steroids; Maintenance with thiopurine, anti-TNF ± thiopurine, or vedolizumab ± immunomodulator
        - Induction therapy: infliximab; Maintenance with infliximab ± thiopurine
        - Induction therapy: IV cyclosporine; Maintenance with thiopurine, anti-TNF ± thiopurine, or vedolizumab ± immunomodulator

**Ankylosing spondylitis (AS)**
2015 ACR/Spondylitis Association of America (SAA)/ Spondyloarthritis Research and Treatment Network (SPARTAN) Recommendations for the treatment of Ankylosing Spondylitis (AS) and Nonradiographic Axial Spondyloarthritis (nr axSpA):[78]

- Stable AS: NSAIDs on demand and physical therapy; there is also a conditional recommendation for TNF inhibitor monotherapy
- Active AS: continuous NSAIDs and physical therapy initially and if disease is still active then add a TNF inhibitor (if patient has concomitant inflammatory bowel disease or recurrent iritis, TNF-i monoclonal antibodies, such as infliximab or adalimumab, are recommended over etanercept). If disease activity still continues, despite adding a TNF, switch to a different TNF inhibitor. Glucocorticoids are not recommended, but may be considered in the event of polyarticular flare of peripheral arthritis, IBD flares, or flares during pregnancy.
- Stable nr-axSpA: NSAIDs on demand and physical therapy with TNF inhibitors conditionally recommended
- Active nr-axSpA: same as active AS but it is recommended that steroids not be used under any circumstance

**Cryopyrin-Associated Periodic Syndromes (CAPS)/Neonatal-Onset Multisystem Inflammatory Disease (NOMID)**
CAPS is a rare disease affecting an estimated 300 people in the United States. CAPS consists of three phenotypically related disorders most often associated with mutations in the CIAS-1/NLRP3 gene, which encodes for cryopyrin.[6,60] Cryopyrin is part of the inflammasone, that when activated, ultimately causes the secretion of IL-1β.[58,59,60] It is estimated that approximately half of CAPS/NOMID patients have the CIAS-1/NLRP3 gene mutation.[6,59,61] The most severe form of CAPS is neonatal onset multisystem inflammatory disorder (NOMID).[61] NOMID presents in neonates with inflammation affecting many organ systems with primary targets of the central nervous system, skin, and joints.[58,61] Prior to the development of interleukin-1 inhibitors, CAPS/NOMID was treated with antihistamines, NSAIDS, corticosteroids, and immunosuppressants.

**Hidradenitis Suppurativa (HS)**
Hidradenitis suppurativa (also known as acne inversa) is rare and prevalence estimates range from less than 1% of the population up to 4%.[73-75] HS is a chronic inflammatory skin condition and pathogenesis is not fully understood; however, it is believed to involve occlusion of the follicular portion of folliculopilosebaceous units (FPSUs).[73] The disease most often involves the intertriginous skin areas (e.g. axillary, groin, perianal, perineal).[73] The clinical manifestations can range from mild to severe symptoms and include inflamed nodules, deep fluctuant abscesses, draining sinus tracts, and bands of severe scar formation. The patient can develop boil-like abscesses that become hard and inflammed with chronic malodorous seepage, which can cause the patient much pain/discomfort and can be psychosocially detrimental.[73-74]

**Uveitis**
Uveitis describes a group of inflammatory diseases that cause swelling in ocular tissues and ultimately destroys the tissue and may lead to vision loss. Despite the name, uveitis can affect more than just the uvea (e.g., lens, retina, vitreous, etc). Uveitis typically is classified by where it occurs in the eye such as anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis uveitis (simultaneous inflammation of the anterior chamber, vitreous humor, and retina or choroid). It also can be described as infectious or noninfectious uveitis. Treatment is based upon the location and severity. Uveitis posterior to the lens is typically not responsive to topical medications. Despite this fact, difluprednate is increasingly being utilized due to its superiority in penetrating the vitreous humor compared to other topical corticosteroids. Other options for treating intermediate uveitis, posterior uveitis, and/or panuveitis, include periocular injection of a glucocorticoid (e.g. triamcinolone) or the risker, but more potent and sustained

benefit option of an intraocular injection of a glucocorticoid (e.g. triamcinolone or a polymer that slowly releases dexamethasone). Patients with refractory inflammation typically are treated with oral glucocorticoids (e.g. 40-60 mg of prednisone/day; 1 mg/kg/day) or other immunosuppressive medications (e.g. azathioprine, mycophenolate, methotrexate, cyclosporine, tacrolimus, cyclophosphamide).[79-82]

**Giant Cell Arteritis (GCA)**
Giant cell arteritis is a vasculitis affecting medium and large vessels. It typically involves the superficial temporal artery and other extracranial branches of the carotid, but can also affect the aorta and its large branches. Patients most commonly experience headaches, but jaw claudication, scalp tenderness, and vision loss can also occur. The gold standard for definitive diagnosis is termporal artery biopsy (TAB), which typically shows focal or segmental inflammatory infiltrates. Glucocorticosteroids are the main treatment for GCA and should be initiated immediately and aggressively. The goal is to suppress inflammation and prevent visual loss and ischemic stroke.[85-86]

**Safety of Biologics**
BSR, BHPR- Guidelines on Safety of Anti-TNF Therapies (2010): Although the guideline does not make any recommendation preferring one drug over the other, the following information was provided.[37]

- Important differences in the risk of latent TB reactivation exist among the first-generation drugs, with the risk being higher with infliximab and adalimumab than with etanercept, a finding confirmed with recently published data from the French and British biologic registries. Data from the BSRBR have shown that the rate of TB was higher with the monoclonal antibodies adalimumab (144 events/100,000 patient –years [pyrs]) and infliximab (136 events/100,000 pyrs) than with etanercept (39 events/100,000 pyrs). After adjustment, the RR compared with etanercept-treated patients was 3.1 (95% CI 1.0, 9.5) for infliximab and 4.2 (95% CI 1.4, 12.4) for adalimumab. TB has been shown to occur sooner after starting infliximab than etanercept. Forty-three per cent of infliximab associated cases occurred during the first 90 days of treatment, a pattern consistent with reactivation of latent infection. In contrast, etanercept-associated TB cases were distributed evenly throughout the reporting period, with only 10% occurring during the first 90 days of treatment.

**REFERENCES**

1. Humira prescribing information. AbbVie. December 2017.
2. Enbrel prescribing information. Amgen. October 2017.
3. Remicade prescribing information. Janssen. October 2015.
4. Cimzia prescribing information. UCB. May 2018.
5. Deleted.
6. Kineret prescribing information. Swedish Orphan Biovitrum AB. May 2016.
7. Orencia prescribing information. E.R. Squibb & Sons. June 2017.
8. Deleted.
9. Simponi prescribing information. Janssen. March 2018.
10. Stelara prescribing information. Janssen. October 2017.

11-29. Deleted.

30. Actemra prescribing information. Genentech. October 2017.
31. Menter A, Korman N, Elmets C, et al. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 10.1016/j.jaad.2008.12.032 (epub February 2009).

32-36. Deleted.

37. Ding T, Ledingham J, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. 2010. doi:10.1093/rheumatology/keq249b.

38-40. Deleted.

41. Ilowite NT. Current treatment of juvenile rheumatoid arthritis. *Pediatrics* 2002; 109:109.
42. Wallace CA. The use of methotrexate in childhood rheumatic diseases. *Arthritis Rheum* 1998; 41:381.
43. Henrickson, M. Efficacy of anakinra in refractory systemic arthritis. *Arthritis Rheum* 2004; 50:S438.
44. Müller K, Herner EB, Stagg A, et al. Inflammatory cytokines and cytokine antagonists in whole blood cultures of patients with systemic juvenile chronic arthritis. *Br J Rheumatol* 1998; 37:562.
45. Mangge H, Schauenstein K. Cytokines in juvenile rheumatoid arthritis (JRA). *Cytokine* 1998; 10:471.
46. Sfikakis PP. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. *Curr Dir Autoimmun* 2010;11:180.
47. Pascual V, Allantaz F, Arce E, et al. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005; 201:1479.
48. Deleted.
49. Deleted.
50. Deleted.
51. Deleted.
52. Xeljanz and Xeljanz XR prescribing information. Pfizer, Inc. May 2018.
53. American College of Rheumatolgoy 2011 Recommendations for the Treatment of Juvenile Idiopathic Arthritis. 2011. *Arthritis Care and Research* 4:1-7.
54. Deleted.
55. Deleted.
56. Gossec, L. et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. December 2015.
57. Simponi ARIA prescribing information. Jansen Biotech, Inc. October 2017.
58. Genetics Home Reference: Neonatal onset multisystem inflammatory disease. Accessed 03/12/2014.
59. A Long-Term Outcome Study With the IL-1 Receptor Antagonist Anakinra/Kineret in Patients With Neonatal Onset Multisystem Inflammatory Disease (NOMID/CINCA Syndrome) A Therapeutic Approach to Study the Pathogenesis of This Disease. Accessed 03/12/2014.
60. Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. *Clinical and Experimental Dermatology*. 2007;33:1-9.
61. Aksentijevich I, Putnam CD, Remmers EF, et al. The clinical continuum of cryopyrinopathies. *Arthritis & Rheumatism*. 2007;56(4):1273-1285.
62. Deleted.
63. Ringold, S., Weiss, P.F., et al. (2013), 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications. *Arthritis & Rheumatism* 65:10:2499-2512
64. *Ann Rheum Dis* doi:10.1136/annrheumdis-2013-204573. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update.
65. Jasvinder A. Singh, Saag, K, et al. Arthritis Care and Research. 2015. 2015 American College of Rheumatology Guideline for the treatment of Rheumatoid Arthritis
66. Deleted.
67. Terdiman, J.P, et al. *Gastroenterology* 2013;145:1459-1463.
68. Entyvio prescribing information. Takeda. May 2014
69-71. Deleted.
72. Cosentyx Prescribing Information. Novartis. January 2016.

73. UpToDate. Pathogenesis, clinical features, and diagnosis of hidradenitis suppurativa (acne inversa). Accessed 9/15/15.
74. NORD. Hidradenitis suppurativa. Accessed 9/15/15.
75. Hidradenitis Suppurativa: Number of Diagnosed Patients, Demographic Characteristics, and Treatment Patterns in the United States. Am J Epidemiol. 2014;179(12):1477-1483.
76. Taltz prescribing information. Eli Lilly and Company. January 2017.
77. Dassopoulos, Themistocles, et al. American Gastroenterological Association: Identification, Assessment and Initial Medical Treatment of Ulcerative Colitis Clinical Care Pathway. 2015.
78. Ward, M. et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Reseach and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis & Rheumatology. 2015.
79. National Institutes of Health: National Eye Institute (NEI). Facts About Uveitis. August 2011. Accessed July 5, 2016.
80. Rosenbaum JT. Uveitis: Treatment. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed July 6, 2016.
81. Wittenberg S. American Academy of Ophthalmology: Ten Clinical Pearls for Treating Uveitis. August 2008. Accessed July 8, 2016.
82. Jabs, D. et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel. American Journal of Ophthalmology. 2000;130:492-513.
83. Inflectra prescribing information. Celltrion. August 2016.
84. Kevzara prescribing information. Regeneron. May 2017.
85. Fraser, Alexander et al. The Treatment of Giant Cell Arteritis. Rev Neurol Dis. 2008 Summer; 5(3): 140-152.
86. UpToDate. Diagnosis of giant cell (temporal) arteritis. Literature review current through April 2017.
87. Siliq prescribing information. Valeant. 02/2017.
88. Tremfya prescribing information. Janssen. 07/2017.
89. Renflexis prescribing information. Merck. 04/2017.
90. Olumiant prescribing information. Eli Lilly and Company. May 2018.