Concomitant (Concurrent) use of Biologics (Biologic Response Modifiers Therapies) and targeted synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs)

Summary

Biologic response modifier therapies, or biologics, are specialized agents bioengineered to interact with specific aspects of the immune system. These unique therapeutics modulate the immune response and disrupt inflammation, playing a pivotal role in managing autoimmune diseases. Biologics, also recognized as immunomodulators and anticytokine agents, have a broad treatment scope encompassing conditions like axial ankylosing spondylitis, graft-versus-host disease, juvenile idiopathic arthritis, rheumatoid arthritis, psoriatic arthritis, psoriasis, and inflammatory bowel disease. Beyond autoimmune disorders, biologics also find usage in oncology, where they can target specific cancer cells or mitigate side effects of other cancer therapies. The administration routes for these drugs include intravenous, subcutaneous, and in some instances, oral delivery.

Classifications of biologics include soluble receptor antagonists, monoclonal antibodies, and cell surface receptor antagonist proteins, defined by their origin and function. Further subclassifications exist based on the mechanism of action and targeted therapy area, such as anti-integrin antibodies, B-cell inhibitors, Interleukin (IL) inhibitors, T-cell inhibitors, and Tumor Necrosis Factor (TNF) inhibitors.

Table 1: Disease-modifying antirheumatic drugs (DMARDs)

Type of DMARD	Generic name	Example brand name(s)	Administration method
Conventional synthetic DMARDs	Azathioprine	Imuran, Azasan	Oral
	Hydroxychloroquine	Plaquenil	Oral
	Leflunomide	Arava	Oral
	Methotrexate	Rheumatrex, Trexall, Otrexup, Rasuvo	Oral or subcutaneous injection
	Sulfasalazine	Azulfidine, Azulfidine EN tabs	Oral
Biologic DMARDs	Abatacept	Orencia	Subcutaneous injection or intravenous infusion
	Adalimumab	Amjevita, Humira	Subcutaneous injection
	Anakinra	Kineret	Subcutaneous injection
	Certolizumab pegol	Cimzia	Subcutaneous injection
	Etanercept	Enbrel	Subcutaneous injection
	Golimumab	Simponi	Subcutaneous injection or intravenous infusion
	Guselkumab	Tremfya	Subcutaneous injection
	Infliximab	Avsola, Inflectra, Remicade, Renflexis	Intravenous infusion
	Ixekizumab	Taltz	Subcutaneous injection
	Risankizumab	Skyrizi	Subcutaneous injection
	Rituximab	Riabni, Rituxan, Ruxience, Truxima	Intravenous infusion

	Sarilumab	Kevzara	Subcutaneous injection
	Secukinumab	Cosentyx	Subcutaneous injection
	Tocilizumab	Actemra	Subcutaneous injection or intravenous infusion
	Ustekinumab	Stelara	Subcutaneous injection
Targeted synthetic DMARDs	Baricitinib	Olumiant	Oral
	Tofacitinib	Xeljanz	Oral
	Upadacitinib	Rinvoq	Oral

NOTE: The above table provides a selection of the commonly prescribed DMARDs in the United States. It is important to note that this table is not exhaustive, and it may not include some recently approved drugs or those currently under investigation.

Definitions

"Concomitant" refers to the simultaneous use of two or more drugs.

Biologic drug class by type of therapeutic molecule/agent:

- **"Soluble receptor antagonists"**are molecules that selectively bind to target cytokines present in the blood, thus preventing the cytokines from interacting with cell surface receptors.
- **"Monoclonal antibodies"**are laboratory-produced antibodies derived from human or nonhuman sources, engineered to target and recognize specific antigens causing disease. Their affinity for antigens is greater than that of soluble receptor antagonists.
- **"Cell surface receptor antagonist proteins"** are inactive proteins that compete with cytokines for binding sites on the cytokine's membrane receptor. They must bind to more than 90 percent of the cell surface receptors to exert their effect effectively.

Biologic response modifier therapies (biologics) drug class by mechanism of action and area of target:

- **"Anti-integrin antibody"** specifically bind to and inhibit the interaction between integrin alpha-4-beta-7 and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in the gut, thus reducing chronic inflammation associated with ulcerative colitis and Crohn's disease. Natalizumab and vedolizumab are FDA-approved anti-integrin drugs.
- **"B-cells inhibitors"** impede the activation of B-cells, the cells initiating a cascade reaction resulting in inflammation. B-cell inhibitors include rituximab and belimumab.

- **"Interleukin (IL) inhibitors"** target interleukins, which are key mediators of inflammation in the body. Anakinra, canakinumab, and rilonacept are common IL-1 inhibitors. IL-6 inhibitors include tocilizumab and sarilumab, while IL-17 inhibitors comprise secukinumab, ixekizumab, or brodalumab. Ustekinumab is a common IL-12/23 inhibitor, and guselkumab and risankizumab are IL-23 inhibitors.
- **"T-cells inhibitors"** impede the activation of cytokines influencing systemic inflammation. An example of a T-cell co-stimulation blocker is abatacept.
- **"Tumor Necrosis Factor (TNF) inhibitors"** specifically target tumor necrosis factor-alpha, an inflammatory cytokine implicated in cell death during inflammation. They halt this inflammatory process and slow disease progression. Examples include infliximab, adalimumab, certolizumab, etanercept, golimumab.

"Disease-modifying antirheumatic drugs (DMARDs)" are a class of drugs that modulate the immune system and inflammation. They are categorized as:

1. Conventional/traditional DMARDs: e.g., methotrexate, sulfasalazine, hydroxychloroquine, leflunomide. They are typically the first line of therapy.
2. Targeted synthetic DMARDs (tsDMARDs): e.g., baricitinib, tofacitinib, apremilast. They are generally prescribed for patients who have failed or have contraindications to conventional DMARDs or biologic DMARDs.
3. Biologic DMARDs: These are the biologics mentioned above, typically used in patients who do not respond to initial therapy for rheumatoid arthritis.

"Kinase inhibitors"are small-molecule drugs not made from recombinant DNA or proteins; thus, they are not considered biologics. They inhibit Janus kinases (JAK), critical for cellular signal transduction pathways. These orally administered medications include tofacitinib and baricitinib.

Policy Statement on Concomitant (Concurrent) use of Biologics (Biologic Response Modifiers Therapies) and targeted synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs)

The concurrent use of two or more biologic agents or a biologic agent with a targeted synthetic DMARD (tsDMARD) for the same diagnosis during the same time period is typically considered experimental or investigational and is not considered medically necessary, unless supported by FDA guidelines, clinical criteria, or high-quality clinical evidence.

- Concomitant use of multiple biologics may increase the risk of infection. Therefore, it is not generally recommended, although some exceptions may apply based on individual patient

conditions, the specific biologics in question, and the most recent clinical evidence and FDA guidelines.

- Clinical trials have not demonstrated added benefit from concomitant use of certain biologics such as B-cell inhibitors with other biologics, IL inhibitors with TNF blockers or other biologic agents, JAK inhibitors with other JAK inhibitors, biologic DMARDs, or potent immunosuppressants, and T-cell co-stimulation blockers with TNF inhibitors, biologic DMARDs, or JAK inhibitors.
- The concomitant use of a phosphodiesterase-4 (PDE4) inhibitor with biologics is also not recommended for certain conditions.
- Concomitant use of TNF inhibitors with other biologic agents, particularly IL inhibitors, has limited supporting evidence and is not recommended.

As the evidence and guidelines change over time, this policy may be updated to reflect the most recent clinical evidence and practice standards. This policy is not exhaustive and exceptions may apply based on individual patient conditions and the latest clinical evidence.

Medical Necessity Criteria for Concomitant (Concurrent) use of Biologics (Biologic Response Modifiers Therapies) and targeted synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs)

The current body of evidence is not sufficient to confirm the medical benefits of concurrent use of Biologic Response Modifiers Therapies (biologics) and targeted synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs). Based on the Plan's review of the available clinical evidence, the Plan maintains the following position:

1. There is not enough information to establish definitive medical necessity criteria for coverage.
2. In line with current evidence, the Plan advises against the concurrent use of biologics and tsDMARDs for the same diagnosis during the same time period, as there is insufficient evidence supporting such practice. This stance prioritizes the safety of our members and directs their treatment towards evidence-based, effective regimens.
3. The concurrent use of these therapies will be classified as experimental, investigational, and unproven until robust clinical evidence suggesting otherwise becomes available.

The Plan considers the concomitant use of various classes of biologic agents including Anti-integrin antibody, B-cell inhibitors, IL inhibitors, and T-cell inhibitors, as well as concomitant use of biologic agents with tsDMARDs, such as JAK inhibitors and PDE4 inhibitors, not medically necessary unless specifically indicated in FDA prescribing guidelines, compendia, national society guidelines, clinical criteria or high-quality clinical evidence.

1. National societies such as the American College of Gastroenterology, American College of Rheumatology, American Academy of Dermatology, National Comprehensive Cancer Network, and National Psoriasis Foundation, currently do not include concurrent use of biologics in their general guidance.
2. FDA prescribing labels often discourage simultaneous usage due to increased risk of severe infections and potential drug interactions.
3. Clinical studies of drugs like Abatacept (Orencia), a T-cell co-stimulation blocker, have failed to demonstrate any enhanced efficacy with concurrent treatment. Instead, patients experienced increased rates of infections and serious infections. The use of TNF inhibitors in conjunction with other biologic agents also lacks compelling evidence supporting its safety and efficacy.

The Plan does not consider medically necessary the concurrent use of a biologic when the following criteria are met:

1. The use of two or more biologic agents (Anti-integrin antibody, B-cell inhibitors, IL inhibitors, T-cell inhibitors, TNF inhibitors), for purposes of the same diagnosis during the same time period (unless indicated that there is greater efficacy with concurrent use of biologics by FDA prescribing guidelines, compendia, national society guidelines, clinical criteria or high-quality clinical evidence); ***or***
2. The use of a biologic agent with a targeted synthetic DMARD (tsDMARD), for purposes of the same diagnosis during the same time period, (unless indicated that there is greater efficacy with concurrent use of biologics by FDA prescribing guidelines, compendia, national society guidelines, clinical criteria or high-quality clinical evidence) for the following, but not limited to:
    a. An oral Janus kinase (JAK) inhibitor (e.g., Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), Xeljanz XR (tofacitinib)); ***or***
    b. An oral phosphodiesterase-4 (PDE4) inhibitor (e.g., Otezla (apremilast)).

NOTE: Oral tsDMARDs coverage is subject to plan benefits and are typically billed through a member's pharmacy benefits.

Experimental or Investigational / Not Medically Necessary

The Plan considers concomitant use of Biologic Response Modifiers Therapies (biologics) and targeted synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs) to be not medically necessary primarily due to lack of substantial high-quality clinical evidence, showing a clear and significant benefit to patients when these treatments are used concurrently.

Most of the current scientific evidence and clinical guidelines advocate for a stepwise approach in the treatment of autoimmune diseases, beginning with conventional synthetic DMARDs, then moving to biologics or tsDMARDs if necessary. The simultaneous use of two or more biologics or a combination of a biologic with a tsDMARD is generally not supported by these guidelines, primarily due to concerns about increased risk of severe side effects, such as serious infections, without a commensurate increase in therapeutic benefit.

The concurrent use of these treatments can also compound their individual side effects, potentially posing increased risk of harm to the patient. As such, until there is clear, robust evidence from well-designed clinical trials showing that the combined use of these treatments offers substantial benefits that outweigh the potential risks, such use will be considered experimental, investigational, and unproven.

Concomitant Use of Biologics

There is limited research of the benefit from use of multiple biologics; the concomitant use of biologics increases the susceptibility to infection. Practice guidelines from national societies such as American College of Gastroenterology, American College of Rheumatology, American Academy of Dermatology, National Comprehensive Cancer Network, National Psoriasis Foundation, do not currently include the concurrent use of biologics (B-cell inhibitors, IL inhibitors, T-cell inhibitors, TNF inhibitors) as part of general guidance. Further guidance can be obtained by FDA prescribing labels for indications and contraindications, warnings and precautions.

Concomitant use of Anti-integrin antibody

The Plan does not consider medically necessary the use of anti-integrin antibodies (e.g., Tysabri (natalizumab), Entyvio (vedolizumab)) concurrently with another Anti-integrin antibody or TNF inhibitors due to risk of drug interactions and increased infections as per prescribing label.

Concomitant use of B-cells inhibitors

Other biologics

The Plan does not consider medically necessary the concomitant use of b-cell inhibitors with other biologics due to limited evidence.

Concomitant Use of IL inhibitors

Other biologics

The Plan does not consider medically necessary the IL inhibitor (e.g., Kineret (anakinra)) with concurrent use of TNF blocker (e.g., infliximab), as there is no added clinical benefit per the FDA

label. IL inhibitor (e.g., ustekinumab) with concurrent use of other biologic agents has not been evaluated in clinical studies of psoriasis.

Concomitant use a of Janus kinase (JAK) inhibitor

The Plan does not consider medically necessary the Rinvoq (upadacitinib) extended-release tablets, Olumiant (baricitinib), Xeljanz (tofacitinib) tablets, Xeljanz (tofacitinib) extended release tablets, or Xeljanz (tofacitinib) Oral Solution concurrently with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine as these combinations are not recommended for use in the prescribing label.

Concomitant Use of T-cell co-stimulation blocker

TNF Inhibitor, Biologic DMARDs, JAK inhibitors

The Plan does not consider medically necessary the T-cell co-stimulation blocker when prescribed with a TNF inhibitor, biologic DMARDs, or Janus kinase inhibitors as it is not recommended as per FDA label. Clinical trials in ORENCIA STUDY IV have failed to show benefit and efficacy of concomitant use of T-cell co-stimulation blocker, Abatacept (Orencia), with TNF inhibitor therapy; the clinical trial showed patients experienced more infections, serious infections, and lack of enhanced efficacy with concurrent treatment.

Concomitant use of Otezla (apremilast)

A phosphodiesterase-4 (PDE4) inhibitor is not recommended for use concurrently with biologics for Behcet's Disease, moderate-to-severe plaque psoriasis, or active psoriatic arthritis, but as an alternative to members who failed or have contraindications to reach therapeutic targets with conventional DMARDs and/or biologics as per Clinical Pharmacology and Lexicomp drug interactions.

***Concomitant** Use of TNF inhibitors*

Other biologics

The Plan does not consider medically necessary the TNF inhibitors (e.g., infliximab, etanercept) when prescribed with another biologic agent such as IL inhibitors (e.g., Kineret) or other biologic agents in different drug classes due to insufficient evidence on concurrent use as per the FDA. Evidence for the treatment of inflammatory bowel disease with TNF inhibitors and concurrent IL inhibitors have been limited to case reports and small case series that raise safety concerns as per Clinical Gastroenterology and Hepatology in 2018.

Applicable Billing Codes (HCPCS/CPT Codes)

Disclaimer

The codes for products listed below are provided for informational purposes only. Inclusion or exclusion of a code does not imply or guarantee coverage or reimbursement by the Plan. The actual coverage or non-coverage of services for an individual member will be determined by the terms and conditions of their policy at the time of service, as well as applicable state and federal law.

For confirmation of coverage, please refer to the member's policy documents, such as the Certificate/Evidence of Coverage, Schedule of Benefits, or Plan Formulary. Alternatively, the Plan can be directly contacted for confirmation. The provision of services is governed by the terms, conditions, and limitations of a member's policy.

As outlined in the aforementioned policy, concurrent use of biologics is not typically considered medically necessary. Coverage for a singular biologic is dependent on the members' plan benefits and adherence to the Plan's Clinical Guidelines, including but not limited to the Commercial Preferred Physician-Administered Specialty Drugs (CG052).

CPT/HCPCS Codes for biologics	
Anti-integrin antibodies	
J2323	Injection, natalizumab, 1 mg
J3380	Injection, vedolizumab, 1 mg
B-cell inhibitors	
Code	*Description*
J0490	Injection, belimumab, 10 mg
J9311	Injection, rituximab 10 mg and hyaluronidase
J9312	Injection, rituximab, 10 mg
IL inhibitors	

C9399/J3590	[Anakinra] Unclassified biologics
C9399/J3590	[Brodalumab] Unclassified biologics
C9399/J3590	[Ixekizumab] Unclassified biologics
C9399/J3590	[Risankizumab] Unclassified biologics
C9399/J3590	[Sarilumab] Unclassified biologics
C9399/J3590	[Secukinumab] Unclassified biologics
J0638	Injection, canakinumab, 1 mg
J1628	Injection, guselkumab, 1 mg
J2793	Injection, rilonacept, 1 mg
J3262	Injection, tocilizumab, 1 mg
J3357	Ustekinumab, for subcutaneous injection, 1 mg
J3358	Ustekinumab, for intravenous injection, 1 mg
T-cell inhibitors	
J0129	Injection, abatacept, 10 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
TNF inhibitors	
J0135	Injection, adalimumab, 20 mg
J0717	Injection, certolizumab pegol, 1 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J1438	Injection, etanercept, 25 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)

J1602	Injection, golimumab, 1 mg, for intravenous use
J1745	Injection, infliximab, excludes biosimilar, 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg
Q5109	Injection, infliximab-qbtx, biosimilar, (Ixifi), 10 mg
Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg
Q5119	Injection, rituximab-pvvr, biosimilar, (RUXIENCE), 10 mg
Q5121	Injection, infliximab-axxq, biosimilar, (AVSOLA), 10 mg
Q5123	Injection, rituximab-arrx, biosimilar, (Riabni), 10 mg
ICD-10 codes considered NOT medically necessary:	
Code	*Description*
Z79	Long term (current) drug therapy
Z79.6	Long term (current) use of immunomodulators and immunosuppressants
Z79.62	Long term (current) use of immunosuppressant
Z79.61	Long term (current) use of immunomodulator
Z79.620	Long term (current) use of immunosuppressive biologic
Z79.622	Long term (current) use of Janus kinase inhibitor

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