

Medical Coverage Policy | Measurement of Serum Antibodies to Selected Biologic Agents



EFFECTIVE DATE: 03/01/2025

POLICY LAST REVIEWED: 03/19/2025

OVERVIEW

Biologic agents used to treat autoimmune diseases include infliximab, adalimumab, vedolizumab, and ustekinumab. Infliximab (Remicade) is an intravenous tumor necrosis factor α blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Adalimumab (Humira) is a subcutaneous tumor necrosis factor α inhibitor that is FDA approved for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, in adults and those with juvenile idiopathic arthritis, hidradenitis suppurativa, and uveitis. Vedolizumab (Entyvio) is an intravenous integrin receptor antagonist that is FDA approved for treatment of ulcerative colitis and Crohn's Disease in adults. Ustekinumab (Stelara) is an intravenous and subcutaneous human interleukin-12 and -23 antagonist that is FDA approved for the treatment of Crohn's disease, and ulcerative colitis in adults, and psoriatic arthritis and plaque psoriasis in children and adults. Following the primary response to these medications, some patients become secondary nonresponders. The development of antidrug antibodies is considered a cause of this secondary nonresponse.

This policy addresses the following tests:

1. Measurement of serum drug levels:
 - Adalimumab CPT Code 80145
 - Infliximab CPT Code 80230
 - Vedolizumab CPT Code 80280
 - Ustekinumab CPT Code 84999
2. Measurement of serum antibodies to drugs
 - Anser IFX (for infliximab; Prometheus Laboratories) CPT Code 84999
 - Anser ADA (for adalimumab; Prometheus Laboratories) CPT Code 84999
 - Anser VDZ (for vedolizumab); Prometheus Laboratories) CPT Code 84999
 - Anser UST (for ustekinumab); Prometheus Laboratories) CPT Code 84999

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

There is no specific CPT coding for the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the

authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

Measurement of serum drug levels: Adalimumab (CPT Code 80145), Infliximab (CPT Code 80230), Vedolizumab (CPT Code 80280) and Ustekinumab (CPT Code 84999)

Measurement of serum drug levels for Adalimumab, Infliximab, Vedolizumab and Ustekinumab is covered.

Medicare Advantage Plans and Commercial Products

Measurement of serum antibodies to drugs: Such as Anser IFX, Anser ADA, Anser VDZ and Anser UST (CPT Code 84999)

Measurement of antidrug antibodies to drugs (e.g. Adalimumab, Infliximab, Vedolizumab and Ustekinumab) in an individual receiving treatment with a biologic agent, either alone or as a combination test which includes the measurement of serum TNF (tumor necrosis factor) blocking agent levels is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Evidence of Coverage for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND

Infliximab, Adalimumab, Vedolizumab, and Ustekinumab in Autoimmune Diseases

Biologic agents (e.g. infliximab, adalimumab, vedolizumab, or ustekinumab) are used to treat multiple inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, inflammatory bowel disease (eg, Crohn disease, ulcerative colitis), ankylosing spondylitis, and plaque psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are typically highly effective for the induction and maintenance of clinical remission. However, not all patients respond, and a high proportion of patients lose response over time. It is estimated that 1 in 3 patients do not respond to induction therapy (primary nonresponse); further, among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to antidrug antibodies (ADA). ADA is also associated with injection-site reactions and acute infusion reactions and delayed hypersensitivity reactions.

Detection of Antidrug Antibodies

The detection and quantitative measurement of ADA is difficult, owing to drug interference and identifying when antibodies likely have a neutralizing effect. First-generation assays (ie, enzyme-linked immunosorbent assays [ELISA]) can measure only ADA in the absence of detectable drug levels, due to the interference of the drug with the assay. Other techniques available for measuring antibodies include the radioimmunoassay

method and, more recently, the homogenous mobility shift assay using high-performance liquid chromatography. Disadvantages of the radioimmunoassay method are associated with the complexity of the test and prolonged incubation time, along with safety concerns related to the handling of radioactive material. The homogenous mobility shift assay measures ADA when infliximab is present in serum. Studies evaluating the validation of results among different assays are lacking, making interstudy comparisons difficult. One retrospective study by Kopylov et al (2012), which evaluated 63 patients, demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with inflammatory bowel disease (ie, double-antigen ELISA and antihuman lambda chain-based ELISA). This study did not include an objective clinical and endoscopic scoring system for validation of results.

Treatment Options for Secondary Nonresponse to Biologic Agents

A diminished or suboptimal response to infliximab, adalimumab, vedolizumab, or ustekinumab can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different biologic agent (in patients who continue to have a loss of response after receiving the increased dose), or switching to a non-biologic agent.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus Laboratories, a College of American Pathologists-accredited lab under the Clinical Laboratory Improvement Amendments, offers four non-radio-labeled, fluid-phase homogenous mobility shift assay tests: called Anser IFX (for infliximab), Anser ADA (for adalimumab), Anser VDZ (for vedolizumab), and Anser UST (for ustekinumab). These tests measure both serum drug concentrations and ADA. They are not based on an ELISA test, and can measure ADA in the presence of detectable drug levels, improving on a major limitation of the ELISA method.

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (eg, Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for serum antibodies to infliximab, adalimumab, vedolizumab, or ustekinumab, the evidence includes multiple systematic reviews, a randomized controlled trials, and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. Antibodies to biologic agents develop in a substantial proportion of treated patients and are believed to neutralize or enhance clearance of the drugs. Considerable evidence has demonstrated an association between antidrug antibodies and secondary nonresponse as well as injection-site and infusion-site reactions. The clinical usefulness of measuring antidrug antibodies hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence has described management changes after measuring antidrug antibodies. A randomized controlled trial did not find a difference in relapse rates with therapeutic drug monitoring of infliximab using trough levels and antidrug antibodies compared to standard therapy without monitoring these levels. A small randomized controlled trial in patients with Crohn's disease comparing antidrug -informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the antidrug antibody -informed approach. Additionally, many assays, some having significant limitations, have been used in studies; antidrug antibody threshold values that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODING

Medicare Advantage Plans and Commercial Products

Measurement of Serum Drug Levels

The following CPT code(s) are considered covered:

80145 Adalimumab
80230 Infliximab
80280 Vedolizumab

At this time, CPT code(s) have not been assigned for the measurement of serum drug levels for Ustekinumab, therefore, the following unlisted code should be used:

84999 Unlisted chemistry procedure

Measurement of Serum Antibodies to Drugs

The following tests are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products. At this time, CPT code(s) have not been assigned to these tests, therefore unlisted CPT code 84999 (unlisted chemistry procedure) should be used:

- Anser IFX
- Anser ADA
- Anser VDZ
- Anser UST

RELATED POLICIES

Biomarker Testing Mandate

Genetic Testing Services

Unlisted Procedures

PUBLISHED

Provider Update, January/May 2025

Provider Update, April 2023, November 2023

Provider Update, April 2022

Provider Update, March 2021

Provider Update, March 2020

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