

Measurement of Serum Antibodies to Selected Biologic Agents

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IMPORTANT REMINDER

The Medicare Advantage Medical Policy manual is not intended to override the member Evidence of Coverage (EOC), which defines the insured's benefits, nor is it intended to dictate how providers are to practice medicine. Physicians and other health care providers are expected to exercise their medical judgment in providing the most appropriate care for the individual member, including care that may be both medically reasonable and necessary.

The Medicare Advantage medical policies are designed to provide guidance regarding the decision-making process for the coverage or non-coverage of services or procedures in accordance with the member EOC and Centers of Medicare and Medicaid Services (CMS) policies and manuals, along with general CMS rules and regulations. In the event of a conflict, applicable CMS policy or EOC language will take precedence over the Medicare Advantage Medical Policy. In the absence of a specific CMS coverage determination for a requested service, item or procedure, the health plan may apply CMS regulations, as well as their Medical Policy Manual or other applicable utilization management vendor criteria developed with an objective, evidence-based process using scientific evidence, current generally accepted standards of medical practice, and authoritative clinical practice guidelines.

Some services or items may appear to be medically indicated for an individual, but may be a direct exclusion of Medicare or the member's benefit plan. Medicare and member EOCs exclude from coverage, among other things, services or procedures considered to be investigational (experimental) or cosmetic, as well as services or items considered not medically reasonable and necessary under Title XVIII of the Social Security Act, §1862(a)(1)(A). In some cases, providers may bill members for these non-covered services or procedures. Providers are encouraged to inform members in advance when they may be financially responsible for the cost of non-covered or excluded services. Members, their appointed representative, or a treating provider can request coverage of a service or item by submitting a pre-service organization determination prior to services being rendered.

DESCRIPTION

Therapy with monoclonal antibodies has revolutionized treatment of patients with inflammatory diseases such as inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]), rheumatoid arthritis and psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are typically highly effective for induction and maintenance of clinical remission.

- Infliximab (Remicade[®], Janssen Biotech, Inflectra[®] by Pfizer, and Renflexis[®] by Merck Sharp & Dohme) is an intravenous tumor necrosis factor alpha (TNF α) blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, CD, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and UC. Infliximab is a chimeric (mouse/human) anti-TNF α monoclonal antibody.

- Adalimumab (Humira® AbbVie) is a subcutaneous TNFα inhibitor that is FDA-approved for treatment of the above indications (CD and UC in adults only) plus juvenile idiopathic arthritis (JIA). Adalimumab is a fully human monoclonal antibody to TNFα.
- Vedolizumab (Entyvio®, Millennium Pharmaceuticals) is an intravenous blocking agent for integrin α4β7 and is FDA-approved for adults with CD or UC.
- Ustekinumab (Stelara®, Janssen Biotech) is an antibody that blocks interleukin IL-12 and IL-23 and is FDA-approved to treat psoriasis and certain patients with CD.
- Certolizumab (Cimzia® by UCB) is a subcutaneous TNFα inhibitor that is FDA-approved for treatment of rheumatoid arthritis, CD, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and non-radiographic axial spondyloarthritis (nr-axSpA).
- Etanercept (Enbrel®, Immunex) is a TNFα inhibitor that is FDA-approved for the treatment of rheumatoid arthritis, JIA, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.
- Golimumab (Simponi® by Janssen Biotech) is a subcutaneous TNFα inhibitor that is FDA-approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, UC, and psoriatic arthritis.

Following primary response to these medications, some patients become nonresponders (secondary nonresponse), and the development of antidrug antibodies (ADA) is considered to be a cause of secondary nonresponse.

MEDICARE ADVANTAGE POLICY CRITERIA

CMS Coverage Manuals*	None
National Coverage Determinations (NCDs)*	None
Noridian Healthcare Solutions (Noridian) Local Coverage Determinations (LCDs) and Articles (LCAs)*	None
Medical Policy Manual	<i>Medicare coverage guidance is not available for the measurement of serum antibodies to any of the biologic agents addressed in this policy. Therefore, the health plan's medical policy is applicable.</i>
	Measurement of Serum Antibodies to Selected Biologic Agents, Laboratory, Policy No. 65 (see "NOTE" below)

NOTE: If a procedure or device lacks scientific evidence regarding safety and efficacy because it is investigational or experimental, the service is noncovered as not reasonable and necessary to treat illness or injury. ([Medicare IOM Pub. No. 100-04, Ch. 23, §30 A](#)). According to Title XVIII of the Social Security Act, §1862(a)(1)(A), only medically reasonable and necessary services are covered by Medicare. In the absence of a NCD, LCD, or other coverage guideline, CMS guidelines allow a Medicare Advantage Organization (MAO) to make coverage determinations, applying an **objective, evidence-based process, based on authoritative evidence**. ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)). The Medicare Advantage Medical Policy - Medicine Policy No. M-149 - provides further details regarding the plan's evidence-assessment process (see Cross References).

MEDICARE AND MEDICAL NECESSITY

To be eligible for Medicare coverage, Medicare requires diagnostic laboratory tests be ordered by the physician who is treating the beneficiary for a specific medical problem and who will use the test results in the management of that specific medical problem.^[1,2] The clinical usefulness of measuring antidrug antibodies (ADA) is based on whether the test results will inform management changes that lead to improved outcomes, as compared with management of symptoms, clinical assessment, and standard laboratory evaluation. Validation of the clinical use of any diagnostic test focuses on analytic validity, diagnostic validity, and clinical utility. Analytic validity demonstrates technical feasibility as compared to a gold standard, including assessment of test reproducibility and precision. Diagnostic utility is evaluated by the ability of a test to accurately predict the clinical outcome in appropriate populations of patients. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a gold standard must be known. Clinical utility is established when the evidence demonstrates that the diagnostic information obtained from a test can be used to benefit patient management and improve health outcomes. Antibodies to these medications are present in a substantial number of patients treated with these medications, and there may be a correlation between the level of these antibodies and clinical response.

REGULATORY STATUS

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

Prometheus[®] Laboratories Inc., a College of American Pathologists–accredited lab under CLIA, offers non-radiolabeled fluid-phase HMSA tests called the Anser[™]IFX test (infliximab), Anser[™]ADA (adalimumab), Anser[®] UST (ustekinumab), and Anser[®] VDZ (vedolizumab). None of these tests are ELISA-based and they can measure antidrug antibodies in the presence of detectable drug levels, improving upon a major limitation of the ELISA method. All tests measure serum concentrations and antidrug antibodies.

LabCorp has a portfolio of tests called DoseASSURE[™] ADL for adalimumab, DoseASSURE[™] UST for ustekinumab, DoseASSURE[™] IFX for infliximab, DoseASSURE[™] CTZ for certolizumab, DoseASSURE[™] ETN for etanercept, and DoseASSURE[™] GOL for golimumab. These tests are Electrochemiluminescence immunoassay (ECLIA) and/or ELISA-based and provide drug concentration and anti-drug antibody levels.

CROSS REFERENCES

[Investigational \(Experimental\) Services, New and Emerging Medical Technologies and Procedures, and Other Non-Covered Services](#), Medicine, Policy No. M-149

REFERENCES

1. [42 CFR §410.32\(a\)](#)
2. Medicare Benefit Policy Manual, Ch. 15 – Covered Medical and Other Health Services, [§80.1 - Clinical Laboratory Services](#)

CODING

Codes	Number	Description
CPT	80299	Quantitation of therapeutic drug, not elsewhere specified
	84999	Unlisted chemistry procedure
	80145	Adalimumab
	80230	Infliximab
	80280	Vedolizumab
HCPCS	None	

***IMPORTANT NOTE:** Medicare Advantage medical policies use the most current Medicare references available at the time the policy was developed. Links to Medicare references will take viewers to external websites outside of the health plan's web control as these sites are not maintained by the health plan.