



BlueCross BlueShield  
of Alabama

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**Name of Blue Advantage Policy:**

**Serum Holotranscobalamin as a Marker of Vitamin B12  
(Cobalamin) Status**

Policy #: 448  
Category: Medicine/Laboratory

Latest Review Date: September 2019  
Policy Grade: **Effective 08/29/2013:**  
**Active Policy but no**  
**longer scheduled for**  
**regular literature**  
**reviews and updates.**

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**BACKGROUND:**

*Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational\*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
  - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
  - *Furnished in a setting appropriate to the patient's medical needs and condition;*
  - *Ordered and furnished by qualified personnel;*
  - *One that meets, but does not exceed, the patient's medical need; and*
  - *At least as beneficial as an existing and available medically appropriate alternative.*

*\*Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare** for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

## **POLICY:**

### **Effective for dates of service on or after November 6, 2010:**

**Blue Advantage** will treat **measurement of holotranscobalamin** as a **non-covered** benefit and as **investigational** in the diagnosis and management of Vitamin B12 deficiency.

*Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

## **DESCRIPTION OF PROCEDURE:**

Holotranscobalamin (holo-TC) is a transcobalamin-vitamin B12 complex which has been investigated as a diagnostic test for vitamin B12 deficiency in symptomatic and at-risk populations, as well as an assay for monitoring response to therapy.

Vitamin B12 is also called cobalamin (Cbl). It is present in foods derived from animal products. IT is an essential vitamin that is required for DNA synthesis affecting red blood cell formation, and methionine synthesis affecting neurological functioning. The endogenous forms of Vitamin B12 include cobalamin and holotranscobalamin, which represent the active fraction of plasma cobalamin. Cobalamin deficiency can result from nutritional deficiencies or malabsorption. Dietary insufficiency is most common among vegetarians and the elderly. Malabsorption of vitamin B12 may be associated with autoantibodies as in pernicious anemia or can occur after gastrectomy, or in other gastrointestinal conditions such as celiac disease, Whipple's disease and Zollinger-Ellison syndrome. Clinical signs and symptoms of cobalamin deficiency include megaloblastic anemia, paresthesias and neuropathy, and psychiatric symptoms such as irritability, dementia, depression, or psychosis. While the hematologic abnormalities disappear promptly after treatment, neurologic disorders may become permanent if treatment is delayed.

The diagnosis of cobalamin deficiency has traditionally been based on low levels of total serum cobalamin, typically less than 200 pg/ml, in conjunction with clinical evidence of disease. However, this laboratory test has been found to be poorly sensitive and specific. Therefore, attention has turned to measuring metabolites of cobalamin as a surrogate marker. For example, in humans only two enzymatic reactions are known to be dependent on cobalamin: the conversion of methylmalonic acid (MMA) to succinyl-CoA, and the conversion of homocysteine and folate to methionine. Therefore, in the setting of cobalamin deficiency, serum levels of MMA and homocysteine are elevated, and have been investigated as surrogate markers.

There also is interest in the direct measurement of the subset of biologically-active cobalamin. Cobalamin in serum is bound to two proteins, transcobalamin and haptocorrin. Transcobalamin-cobalamin complex (called holotranscobalamin, or holo-TC) functions to transport cobalamin from its site of absorption in the ileum to specific receptors throughout the body. Less than 25%

of the total serum cobalamin exists as holo-TC, but this is considered the clinically relevant biologically active form. Serum levels of holo-TC can be measured using a radioimmunoassay or enzyme immunoassay.

## **KEY POINTS:**

This policy is based on a review of current literature as of September 23, 2019.

### **Summary of Evidence**

Holotranscobalamin (holo-TC) is a transcobalamin-vitamin B12 complex that has been investigated as a diagnostic test for vitamin B12 deficiency in symptomatic and at-risk populations, as well as an assay for monitoring response to therapy. Holo-TC seems more suitable than total vitamin B-12 for the diagnosis of vitamin B-12 deficiency. There is currently no gold standard or true reference method to diagnose subtle vitamin B-12 deficiency, which makes evaluation of the clinical usefulness of holoTC and the estimation of sensitivity and specificity problematic. There is a need for studies that can prove or disprove this technology's clinical utility. Evidence of the clinical utility of the test is currently lacking, and therefore is considered investigational.

### **Practice Guidelines and Position Statements**

Many societies have recommended vitamin B12 supplementation for specific clinical conditions or evaluation for vitamin B12 deficiency in the workup for clinical indication without specifying a methodology. An exception is in a practice parameter for peripheral neuropathy by the American Academy of Neurology (AAN), who has specified a methodology (evidence level C): "serum B12 level with metabolites (methylmalonic acid with or without homocysteine)" in the evaluation for vitamin B12 deficiency.

### **U.S. Preventive Services Task Force Recommendations**

Not applicable.

## **KEY WORDS:**

Holo-TC, Vitamin B12 Deficiency, Holotranscobalamin, Transcobalamin, Axis-Shield, HoloTC RIA

## **APPROVED BY GOVERNING BODIES:**

In January 2004, the device "HoloTC RIA" (Axis-Shield plc, Dundee, UK) is an example of a radioimmunoassay for holo-TC that was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for use in:

"Quantitative measurement of the fraction of cobalamin (vitamin B12) bound to the carrier protein transcobalamin in the human serum or plasma. Measurements obtained by this device are used in the diagnosis and treatment of vitamin B12 deficiency."

In November 2006, the device “Axis-Shield HoloTC Assay” (Axis-Shield, Dundee, UK), an enzyme immunoassay for holo-TC, was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for use in:

“Quantitative determination of holotranscobalamin...in human serum and plasma on the AxSym® System. HoloTC is used as an aid in the diagnosis and treatment of vitamin B12 deficiency.”

**BENEFIT APPLICATION:**

Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

Pre-certification requirements: Not applicable

**CURRENT CODING:**

CPT Codes:

84999	Unlisted chemistry procedure.
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**REFERENCES:**

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## **POLICY HISTORY:**

Adopted for Blue Advantage, September 2010

Available for comment September 22-November 5, 2010

Medical Policy Group, October 2012

Medical Policy Group, August 2013

**Effective August 29, 2013: Active Policy but no longer scheduled for regular literature reviews and updates.**

Medical Policy Group, December 2015

Medical Policy Group, September 2019

*This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*