Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/16**
(See policy history boxes for previous effective dates)

Title: Intravenous Immune Globulin (IVIG) for Recurrent Early Pregnancy Loss

Description / Background

Human immune globulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral antigens. Three formulations of human IgG are available for delivery by intravenous infusion (IVIg), by subcutaneous infusion (SCIg), or by intramuscular (IMIg) depot injections. IMIg has been largely abandoned in the United States because volume constraints and pain preclude delivery of sufficient product weekly into each buttock to yield therapeutic serum levels of IgG, leaving recipients susceptible to infections. Thus, this policy focuses on IVIg and SCIg for conditions that typically would be treated in an outpatient setting.

IVIg is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVIg has been used to correct immune deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. Several IVIg products are available for clinical use in the United States.

This policy only addresses nonspecific pooled preparations of IVIg; it does not address other immunoglobulin preparations that are specifically used for passive immunization to prevent or attenuate infection with specific viral diseases such as respiratory syncytial virus, cytomegalovirus, or hepatitis B.

Recurrent spontaneous abortion (RSA) is defined as 3 or more pregnancies resulting in a spontaneous abortion prior to 16 to 20 weeks of gestational age. Patients with RSA frequently have immunologic abnormalities, particularly antiphospholipid antibodies whose incidence may increase with each subsequent pregnancy loss. Because these antibodies are associated with clotting abnormalities, treatment has included aspirin and heparin. Other more subtle immune etiologies have also been investigated. For example, a variety of cytokines and other mediators may be toxic to the conceptus. These cytokines may be detected in an embryo cytotoxicity

assay in which activated lymphocytes from women with RSA are shown to be toxic to placental cell lines. Elevated levels of natural killer cells, which may be associated with antiphospholipid antibodies, have also been implicated in RSA. Another theory proposes that a lack of maternal blocking antibodies to prevent immunologic rejection of the fetus may be responsible. IVIg has been explored as a treatment based on its ability to influence both T- and B-cell function. In fact, IVIg may be offered to those patients with antiphospholipid antibodies without a prior history of RSA who are currently pregnant or contemplating pregnancy.

Regulatory Status

Several IVIg products have been approved by FDA. These include Carimune® (ZLB Bioplasma), Flebogamma® (Grifols), Gammagard® (Baxter), Gamunex-C® (Grifols), Octagam® (Octapharma), Polygam® S/D (Baxter) Privigen® (CSL Behring LLC) and BIVIGAM™ (Biotest Pharmaceuticals).

Several SCIg products have received FDA marketing approval for primary immunodeficiencies. These include Vivaglobin® (ZLB Behring LLC, Kankakee, IL), Hizentra® (ZLB Behring LLC, Kankakee, IL), Gamunex-C® (Grifols), and Gammaked® (Kedrion Biopharma, Cambridge, MA).

Medical Policy Statement

The safety and effectiveness of IVIG for the treatment of recurrent early pregnancy loss have not been clinically proven. The use of immune globulin therapy is considered experimental/investigational for the treatment of recurrent spontaneous abortion.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

90283	J1459	J1557	J1559	J1561
J1566	J1568	J1569	J1572	J1599

Rationale

A 2006 Cochrane systematic review of various immunotherapies for treating recurrent miscarriage concluded that IVIg provides no significant beneficial effect over placebo in preventing further miscarriages.

A blinded RCT (Jablonowska et al 1999) of 41 women treated with IVIg or saline placebo found no differences in live birth rates.

A multicenter RCT (Branch et al 2000) comparing heparin and low-dose aspirin with versus without IVIg in women with lupus anticoagulant, anticardiolipin antibody, or both, found no significant differences.

In addition, a RCT (Christiansen et al 2002) of 58 women with at least 4 unexplained miscarriages tested IVIg versus placebo and analyzed results by intention to treat. The live birth rate was the same for both groups; also, there was no difference in neonatal data.

Other nonrandomized but controlled trials also report no benefit for IVIg treatment. There is insufficient evidence in RCTs or other trials to support benefit in secondary (live birth followed by consecutive spontaneous abortions) versus primary (no prior live births) spontaneous abortions. A variety of immunologic tests may precede the initiation of IVIg therapy. These tests, including various subsets of lymphocytes, human leukocyte antigen (HLA) testing, and lymphocyte functional testing (ie, natural killer cell assays and the embryo cytotoxicity test), are research tools that explore subtle immunologic disorders that may contribute to maternal immunologic tolerance of the fetus. However no clinical data show that the results of these tests can be used in the management of patients to reduce the incidence of recurrent spontaneous abortion, particularly because IVIg therapy has not been shown to be an effective therapy.

In 2006, the American Society of Reproductive Medicine concluded that "For the management of recurrent spontaneous pregnancy loss IVIG is an experimental treatment."

Government Regulations

National/Local:

There is no national or local Medicare policy related to intravenous immune globulin use in early pregnancy loss.

Michigan Department of Health and Human Services:

Medicaid would review on an individual basis with medical documentation required.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Intravenous Immune Globulin Therapy

References

1. American Society of Reproductive Medicine. Intravenous Immunoglobulin (IVIG) and Recurrent Spontaneous Pregnancy Loss: A Practice Committee Report; A Committee Opinion. 2006. Retrieved from https://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Committee_Opinions/intravenous_immunoglobulin(1).pdf (3/7/16)
2. Branch DW, Peaceman AM, Druzin M et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. Am J Obstet Gynecol 2000; 182(1 pt 1):122-7.
3. Christiansen OB, Pedersen B, Rosgaard A et al. A randomized, double-blind, placebo-controlled trial of intravenous immunoglobulin in the prevention of recurrent miscarriage: evidence for a therapeutic effect in women with secondary recurrent miscarriage. Hum Reprod 2002; 17(3):809-16.
4. Jablonowska B, Selbing A, Palfi M et al. Prevention of recurrent spontaneous abortion by intravenous immunoglobulin: a double-blind placebo-controlled study. Hum Reprod 1999; 14(3):838-41.
5. Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database Syst Rev 2006; (2):CD000112.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 3/7/16, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/24/05	1/24/05	6/29/04	Joint policy established
9/1/06	7/10/06	7/6/06	Routine maintenance
11/1/08	8/19/08	10/30/08	Routine maintenance
5/1/12	2/21/12	2/21/12	Routine maintenance
7/1/15	4/24/15	5/8/15	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance Policy retired

Next Review Date: Policy retired; procedure is being managed by Pharmacy

BLUE CARE NETWORK BENEFIT COVERAGE POLICY: INTRAVENOUS IMMUNE GLOBULIN (IVIG) FOR RECURRENT EARLY PREGNANCY LOSS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Refer to the Medicaid information under the Government Regulations section of this policy.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.