Chronic Intermittent Intravenous Insulin Therapy (CIIIT)

Policy # 00015
Original Effective Date: 06/05/2002
Current Effective Date: 06/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers chronic intermittent intravenous insulin therapy (CIIIT), also known as intermittent intravenous insulin therapy, outpatient intravenous insulin therapy (OIVIT), cellular activation therapy (CAT), intercellular activation therapy (iCAT), hepatic activation therapy (HAT), metabolic activation therapy (MAT), pulse insulin therapy (PIT), pulsatile intravenous insulin therapy (PIVIT), pulsatile therapy (PT), Trina Health artificial pancreas treatment, physiologic insulin resensitization therapy (PIR) to be **investigational.***

Policy Guidelines

This policy does not apply to use of intravenous insulin infusions in the inpatient setting (ie, for the treatment of diabetic ketoacidosis or diabetic hyperosmolar coma).

Background/Overview

Glucose Homeostasis

Insulin-mediated glucose homeostasis involves 3 primary functions that occur at 3 locations: (1) insulin secretion by the pancreas; (2) glucose uptake, primarily in the muscle, liver, gut, and fat; and (3) hepatic glucose production. In the fasting state, when insulin levels are low, most glucose uptake into cells is non-insulin-mediated. Glucose uptake is then balanced by the liver production of glucose. However, after a glucose challenge, insulin binds to specific receptors on the hepatocyte to suppress glucose production. Without this inhibition, marked hyperglycemia may result.

Medications for Glucose Homeostasis in Diabetes

Diabetes is characterized by elevated blood glucose levels due to inadequate or absent insulin production (type 1 diabetes) or due to increased hepatic glucose production, decreased peripheral glucose uptake, and decreased insulin secretion (type 2 diabetes).

Patients with type 1 diabetes require insulin therapy. Insulin therapy for patients with type 1 diabetes usually consists of multiple daily subcutaneous injections with both basal and mealtime insulin or continuous subcutaneous insulin infusions given through an insulin pump. Insulin therapy has improved over the last several decades with newer insulin products providing improved

pharmacokinetic parameters to closer mimic physiologic insulin. Intravenous insulin is used in the acute inpatient setting to manage hyperglycemic emergencies (eg, diabetic ketoacidosis).

Interventions
The therapy being considered is CIIIT. Several forms of CIIIT, in which insulin is delivered intravenously or into the peritoneal space, have been evaluated.

CIIIT—also referred to as outpatient intravenous insulin therapy, pulsatile intravenous insulin therapy, hepatic activation therapy, or metabolic activation therapy—involves delivering insulin intravenously once weekly over several hours in a pulsatile fashion using a specialized pump controlled by a computerized program that adjusts the doses based on frequent blood glucose monitoring. CIIIT is principally designed to normalize the hepatic metabolism of glucose. Currently, no studies have been identified that have investigated the proposed mechanism of action of CIIIT in humans.

Aoki et al (1993) proposed that, in patients with type 1 diabetes, lower levels of insulin in the portal vein are associated with a decreased concentration of the liver enzymes required for hepatic metabolism of glucose. The authors stated: "We reasoned that if the liver of an Insulin-Dependent Diabetes Mellitus [ie, type 1 diabetes] patient could be perfused with near-normal concentrations of insulin during meals, the organ could be reactivated," and proposed that intermittent intravenous pulsatile infusions of insulin administered once weekly while the patient ingests a carbohydrate meal would increase the portal vein concentrations of insulin, ultimately stimulating the synthesis of glucokinase and other insulin-dependent enzymes. The pulses are designed to deliver a higher, more physiologic concentration of insulin to the liver than is delivered by traditional subcutaneous injections. This higher level of insulin is thought to more closely mimic the body's natural levels of insulin because it is delivered to the liver. The goal of this outpatient therapy is improved glucose control through improved hepatic activation.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Any insulin infusion pump can be used for chronic intermittent intravenous insulin therapy. Infusion pumps have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for the delivery of intravenous medications. FDA product code: lZG.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Description
Chronic intermittent intravenous insulin therapy (CIIIT) is a technique for delivering variable-dose insulin to diabetic patients with the goal of improved long-term glycemic control. Through an unknown mechanism, CIIIT is postulated to induce insulin-dependent hepatic enzymes to suppress glucose production.

Summary of Evidence
For individuals who have type 1 diabetes who receive chronic intermittent intravenous insulin therapy (CIIIT), the evidence includes 2 randomized controlled trials (RCTs) and several uncontrolled studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. A limited number of uncontrolled studies have suggested that CIIIT might improve glycemic control. The 2 RCTs have reported that CIIIT might moderate the progression of nephropathy or retinopathy. However, the published studies were small and reported improvements on intermediate outcomes only (ie, changes in laboratory values). The clinical significance of the differences reported in these trials is uncertain. Additionally, most published evidence appeared between 1993 and 2010 and, as a result, does not account for improvements in diabetes care. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in Supplemental Information if they were issued by, or jointly by, a U.S. professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Diabetes Association
The 2025 American Diabetes Association "Standards of Care in Diabetes" includes the American Diabetes Association's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate the quality of care. There is no mention of chronic intermittent intravenous insulin therapy (CIIIT).

American Association of Clinical Endocrinology
In 2022, the American Association of Clinical Endocrinology updated its 2015 clinical practice guideline for developing a diabetes mellitus comprehensive care plan. The guideline includes evidence-based recommendations for the comprehensive care of people with both type 1 and type 2 diabetes; recommendations are divided up into 4 sections: screening, diagnosis, targets, and monitoring; comorbidities and complications; management; education and new topics regarding diabetes. There is no mention of CIIIT.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The 2009 Centers for Medicare & Medicaid Services issued a decision memo on the use of outpatient intravenous insulin therapy, which stated:

> "Effective … 2009, the Centers for Medicare and Medicaid Services (CMS) determines that the evidence is adequate to conclude that OIVIT [outpatient intravenous insulin therapy] does not improve health outcomes in Medicare beneficiaries. Therefore, CMS determines that OIVIT is not reasonable and necessary…. Services comprising an Outpatient Intravenous Insulin Therapy regimen are nationally non-covered under Medicare when furnished pursuant to an OIVIT regimen…."

Ongoing and Unpublished Clinical Trials
A search for active or recruiting clinical trials in December 2024 did not yield results for trials that might influence this review.

References

1. ElSayed NA, McCoy RG, Aleppo G, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2025. Diabetes Care. Jan 01 2025; 48(Supplement_1): S181-S206. PMID 39651989
2. Mirbolooki MR, Taylor GE, Knutzen VK, et al. Pulsatile intravenous insulin therapy: the best practice to reverse diabetes complications?. Med Hypotheses. Sep 2009; 73(3): 363-9. PMID 19446964
3. Aoki TT, Benbarka MM, Okimura MC, et al. Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus. Lancet. Aug 28 1993; 342(8870): 515-8. PMID 8102666
4. Aoki TT, Grecu EO, Arcangeli MA. Chronic intermittent intravenous insulin therapy corrects orthostatic hypotension of diabetes. Am J Med. Dec 1995; 99(6): 683-4. PMID 7503093
5. Aoki TT, Grecu EO, Prendergast JJ, et al. Effect of chronic intermittent intravenous insulin therapy on antihypertensive medication requirements in IDDM subjects with hypertension and nephropathy. Diabetes Care. Sep 1995; 18(9): 1260-5. PMID 8612440
6. Weinrauch LA, Sun J, Gleason RE, et al. Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 diabetes mellitus. Metabolism. Oct 2010; 59(10): 1429-34. PMID 20189608
7. Dailey GE, Boden GH, Creech RH, et al. Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy. Metabolism. Nov 2000; 49(11): 1491-5. PMID 11092517
8. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. Oct 2022; 28(10): 923-1049. PMID 35963508
9. Centers for Medicaid & Medicare Services. National Coverage Determination (NCD) for Outpatient Intravenous Insulin Treatment (40.7). 2009; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=334.

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04/18/2002	Medical Policy Committee review
06/05/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy
06/01/2004	Medical Director review
06/15/2004	Medical Policy Committee review. Format revision. No substance change to policy.
06/28/2005	Managed Care Advisory Council approval
03/01/2005	Medical Director review
03/15/2005	Medical Policy Committee review
04/04/2005	Managed Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
04/04/2007	Medical Director review
04/18/2007	Medical Policy Committee approval. CMS information added. Coverage eligibility unchanged.
03/04/2009	Medical Director review
03/18/2009	Medical Policy Committee approval. No change to coverage.
03/05/2010	Medical Policy Committee review
03/19/2010	Medical Policy Implementation Committee approval. No change to coverage.
03/03/2011	Medical Policy Committee review
03/16/2011	Medical Policy Implementation Committee approval. No change to coverage.
03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/07/2013	Medical Policy Committee review
03/20/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/06/2014	Medical Policy Committee review
03/19/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2016	Coding update
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017	Medical Policy Committee review

05/17/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/20/2022	Coding update
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. Expanded investigational statement to include other forms of chronic intermittent intravenous insulin therapy (CIIIT).
05/01/2025	Medical Policy Committee review
05/13/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2026

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	96365, 96366
HCPCS	G9147, J1817
ICD-10 Diagnosis	All Related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company

recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.