Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/22**
(See policy history boxes for previous effective dates)

Title: Chronic Intermittent Intravenous Insulin Therapy (CIIIT)

Description/Background

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

Glucose Homeostasis

There are 3 main sites of insulin-mediated glucose homeostasis that must function in a coordinated fashion to maintain euglycemia: 1) insulin secretion by the pancreas; 2) glucose uptake, primarily in the muscle, liver, gut, and fat; and 3) hepatic glucose production. For example, in the fasting state, when insulin levels are low, the majority of glucose uptake is noninsulin mediated. Glucose uptake is then balanced by liver production of glucose, critical to nourish vital organs, such as the brain. However, after a glucose challenge, insulin binds to specific receptors on the hepatocyte to suppress glucose production. Without this inhibition, as can be seen in diabetic patients, marked hyperglycemia may result.

Medications Used 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 a state of increased hepatic glucose production, decreased peripheral glucose uptake, and decreased insulin secretion (type 2 diabetes).

Different classes of diabetic drug therapy target different aspects of glucose metabolism. Various insulin secretagogues (i.e., sulfonylureas) function by increasing the pancreatic secretion of insulin; thiazolidinediones (i.e., pioglitazone [Actos®] and rosiglitazone [Avandia®]) function in part by increasing glucose uptake in the peripheral (principally skeletal) tissues; and biguanides (i.e., metformin) function by decreasing hepatic glucose production. While patients with type 2 diabetes may be treated with various combinations of all 3 of the above classes of drugs, patients with type 1 diabetes who have no baseline insulin secretion may receive exogenous insulin therapy, with or without additional drug therapy with

thiazolidinediones or metformin. Intravenous insulin is used in the acute inpatient setting for the management of hyperglycemic emergencies (i.e., diabetic ketoacidosis).

Chronic Intermittent Insulin Therapy
CIIIT, also referred to as outpatient intravenous insulin therapy (OIVIT); pulsatile intravenous insulin therapy; hepatic activation; or metabolic activation, involves delivering insulin intravenously over a 6- to 7-hour period in a pulsatile fashion using a specialized pump controlled by a computerized program that adjusts the dosages based on frequent blood glucose monitoring. CIIIT therapy is principally designed to normalize the hepatic metabolism of glucose.

CIIIT is typically delivered once weekly as outpatient therapy.

Regulatory Status

Any insulin infusion pump can be used for the purposes of CIIIT. Infusion pumps have received U.S. Food and Drug Administration (FDA) marketing clearance through the 510(k) process, as they are determined to be substantially equivalent to predicate devices for the delivery of intravenous medications. FDA product code: IZG.

Medical Policy Statement

Chronic intermittent intravenous insulin therapy (CIIIT), either pulsatile or continuous, is experimental/investigational. It has not been scientifically demonstrated to be an effective adjunct to conventional treatment for diabetes mellitus.

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.):

G9147

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. Following is a key summary of the literature to date, which primarily addresses whether chronic intermittent intravenous insulin therapy (CIIIT) improves glycemic control in diabetic patients and whether CIIIT reduces end organ damage associated with diabetes. No studies were identified that investigate the proposed mechanism of action of CIIIT in humans.

CIIIT FOR TYPE 1 DIABETES

Clinical Context and Test Purpose

The purpose of CIIIT in patients who have Type 1 diabetes mellitus is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does the use of CIIIT used to treat patients with Type 1 diabetes mellitus improve net health outcomes?

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest are patients with Type 1 diabetes mellitus who need improved glycemic control.

Interventions

The therapy being considered is CIIT. Several forms of chronic intermittent insulin therapy, 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.[1] They stated: "We reasoned that if the liver of an IDDM [insulin-dependent diabetes mellitus; i.e., 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 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.

Comparators
The following therapies and practices are currently being used to make decisions about treatment to maintain normogylcemia in patients with Type 1 diabetes mellitus: guideline directed diabetic medical therapy including subcutaneous insulin as well as diabetes self-management with glucose monitoring, diet and exercise regimens.

Outcomes
The general outcomes of interest are symptomatic hyperglycemia and hypoglycemia, disease status changes such as the development of end-organ damage and treatment-related morbidity.

Patients with Type 1 diabetes mellitus require lifelong medical monitoring of glycemic control and end-organ status. Informal publication has indicated that patients have been treated with CIIIT for as long as 12 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Glycemic Control

In 1993, Aoki et al published a case series of 20 patients with "brittle" type 1 diabetes.[1] All patients received 4 daily injections of insulin (type of insulin not described); additional oral drug therapy, if any, was not described. Throughout the study, patients remained in close contact with the clinic (at least once a week), during which appropriate adjustments in diet, insulin therapy, and activity were made. While the study reported a decrease in the HbA_{1c} levels, the lack of a control group limits the interpretation of results. For example, the intense follow-up of the patients could have impacted results, regardless of any possible effects of the CIIIT.[1, 2]

Aoki et al also examined the effect of CIIIT with hypertensive medications in 26 patients with type 1diabetes and associated hypertension and nephropathy.[3] The 26 patients were randomly assigned to a control group or treatment group for 3 months and then crossed over to the opposite group for an additional 3 months. At baseline, all patients were being treated with 4 daily insulin injections and had achieved acceptable HbA_{1c} levels of 7.4%. Patients also achieved acceptable baseline blood pressure control (<140/90 mm Hg) with a variety of medications (i.e., angiotensin converting enzyme inhibitors, calcium channel blockers, loop diuretics, and alpha-2 agonists). While the study was randomized, it was not blinded in that sham CIIIT procedures were not performed. Therefore, those patients receiving CIIIT received more intense follow-up during this period. During the treatment phase, patients reported a significant decrease in dosage of antihypertensive medicines. No difference in glycemic control was noted. Because all patients had adequate blood pressure control at baseline, the clinical significance of the decrease in antihypertensive dosage requirement associated with CIIIT is uncertain.

Section Summary: Glycemic Control

One nonblinded RCT and 1 cases series reporting on the effect of CIIT on glycemic control in type 1 diabetic patients were identified. Both studies reported improvements: one in HbA_{1c} compared with baseline, and the other in dose of antihypertensive medication in the treatment group compared with control. However, the lack of a blinded control comparator group in the RCT limits the conclusions that can be drawn.

Reductions in Diabetic End-Organ Damage

In 2010, Weinrauch et al published a study of the effects of CIIIT on progression of nephropathy and retinopathy in 65 subjects with type I diabetes.[4] Patients were randomly allocated to standard therapy of 3 to 4 daily subcutaneous insulin injections (n=29) or standard therapy plus weekly CIIIT (n=36). Baseline demographic characteristics were similar between the 2 groups, as were age of onset, duration of diabetes, diabetic control, and renal function (average creatinine, 1.59 mg/dL; average creatinine clearance, 60.6 mL/min). Primary end points were progression of diabetic retinopathy and nephropathy. There was no significant difference in progression of diabetic retinopathy. Progression was noted in 18.8% of 122 eyes that were adequately evaluated (17.9% of 67 treated eyes, 20.0% of 55 controls; p=0.39). On average, serum creatinine increased in both groups; the increase was less in the treatment group (0.09 mg/dL vs. 0.39 mg/dL, respectively; p=0.035). While average creatinine clearance fell less in the treatment group, the difference was not significant (-5.1 mL/min vs. -9.9 mL/min, respectively; p=0.30). Glycemic control did not vary significantly. The clinical significance of the difference in creatinine levels is uncertain.

In 2000, Dailey et al reported on the effect of CIIIT on the progression of diabetic nephropathy.[5] A total of 49 patients with type 1 diabetes were included. Of these, 26 were assigned to the control group, and 23 were assigned to the treatment group that underwent weekly CIIIT. Both groups reported a significant decrease in HbA_{1c} during the 18-month study period. The creatinine clearance declined in both groups as expected, but the rate of decline in the treatment group was significantly less compared with the control group. Again, the clinical significance of this finding is uncertain; larger clinical trials that look at the end point of time to progression of renal failure are needed.

Section Summary: Reductions in Diabetic End-Organ Damage
Two controlled studies focusing on the efficacy of CIIIT for reducing diabetic end-organ complications were identified. Both reported significant improvements in intermediate measures of glycemic control in each group from pre- to post intervention, but did not consistently report differences in clinically meaningful outcomes from the beginning of the studies to the end. Similarly, there were no significant differences between treatment groups in the RCT.

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 and several uncontrolled studies. Relevant outcomes are symptoms and change in disease status. A limited number of uncontrolled studies suggest that CIIIT may improve glycemic control. Two randomized trials report that CIIIT may moderate the progression of nephropathy and/or retinopathy. However, the published studies are small and report benefits on intermediate outcomes only (i.e., changes in laboratory values). The clinical significance of the differences reported in the studies is uncertain. Additionally, most published evidence appeared between 1993 and 2000 and as a result, does not account for more recent improvements in diabetes care. The evidence is insufficient to determine the effects of the technology on health outcomes.

ONGOING CLINICAL TRIALS

A search for active or recruiting clinical trials did not yield results for trials that might influence this review.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Diabetes Association

The 2021 American Diabetes Association's "Standards of Medical 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.[6]

U.S. Preventive Services Task Force Recommendations

CIIIT is not a preventive service.

Government Regulations

"Effective for claims with dates of service on and after December 23, 2009, the Centers for Medicare and Medicaid Services (CMS) determines that the evidence is adequate to conclude that outpatient intravenous insulin therapy (OIVIT, i.e., CIIIT) does not improve health outcomes in Medicare beneficiaries. Therefore, CMS determines that OIVIT is not reasonable and necessary for any indication under section 1862(a)(1)(A) of the Social Security Act. Services comprising an Outpatient Intravenous Insulin Therapy regimen are nationally non-covered under Medicare when furnished pursuant to an OIVIT regimen (see subsection A. above)."[11]

Local:

No local coverage determination on this topic.

(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

- Intermittent (72 Hour) or Continuous Invasive Glucose Monitors
- Continuous Subcutaneous Insulin Infusion Pumps
- Artificial Pancreas Device Systems

References

1. Aoki TT, Benbarka MM, Okimura MC et al. Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus. Lancet 1993; 342(8870):515-8.
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4. Dailey GE, Boden GH, Creech RH et al. Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy. Metabolism 2000; 49(11):1491-5.
5. 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 2010.
6. Handelsman Y, Mechanick JI, Blonde L et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2011; 17 Suppl 2:1-53.
7. Rodbard HW, Blonde L, Braithwaite SS et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007; 13 Suppl 1:1-68.

8. American Diabetes Association. Clinical Practice Recommendations 2009. Diabetes Care 2009; 32(suppl 1). Available online at: http://care.diabetesjournals.org/content/32/Supplement. Last accessed January 2022.
9. Qaseem A, Humphrey LL, Chou R et al. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011; 154(4):260-7.
10. Kansagara D, Fu R, Freeman M et al. Intensive insulin therapy in hospitalized patients: a systematic review. Ann Intern Med 2011; 154(4):268-82.
11. Centers for Medicare & Medicaid Services (CMS), *National Coverage Determination NCD) for Outpatient Intravenous Insulin Treatment (40.7),* available at < https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=334&ncdver=1&bc=AAAAQAAAAAAA& > (January 2022).
12. Blue Cross Blue Shield Association. Chronic Intermittent Intravenous Insulin Therapy (CIIIT). Medical Policy Reference Manual. Policy #2.01.43, Issue 7:2013, original policy date 11/20/01, last review date March 2021.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/10	7/22/10	6/15/10	Joint policy established
5/1/12	2/21/12	2/21/12	Routine maintenance; updated rationale, verified references.
11/1/13	8/22/13	8/27/13	Routine maintenance; references and rationale updated.
5/1/15	2/17/15	2/27/15	Routine maintenance Editorial revisions made to background and rationale Added references 9-10
5/1/16	2/16/16	2/16/16	Routine maintenance. No change in policy status.
5/1/17	2/21/17	2/21/17	Routine policy maintenance. No change in policy status.
5/1/18	2/20/18	2/20/18	Routine policy maintenance. No change in policy status.
5/1/19	2/19/19		Routine policy maintenance. No change in policy status.
5/1/20	2/18/20		Routine policy maintenance. No change in policy status.
5/1/21	2/16/21		Routine policy maintenance. No change in policy status.
5/1/22	2/15/22		Routine maintenance

Next Review Date: 1st Qtr. 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CHRONIC INTERMITTENT INTRAVENOUS INSULIN THERAPY (CIIIT)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A