Chronic Intermittent Intravenous Insulin Therapy (CIIIT)

Policy # 00015
Original Effective Date: 06/05/2002
Current Effective Date: 05/17/2017

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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 (CIIIT) therapy to be investigational.*

Background/Overview
Chronic intermittent intravenous insulin therapy 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
Insulin-mediated glucose homeostasis involves 3 primary functions which 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 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 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 (eg, sulfonylureas) function by increasing the pancreatic secretion of insulin; thiazolidinediones (eg, pioglitazone [Actos®], rosiglitazone [Avandia®]) function in part by increasing glucose uptake in the peripheral (principally skeletal) tissues; and biguanides (eg, metformin) function by decreasing hepatic glucose production. While patients with type 2 diabetes may be treated with various combinations of all 3 of these classes of drugs, with or without additional insulin, patients with type 1 diabetes, who have no baseline insulin secretion, receive exogenous insulin therapy. Standard insulin management involves use of subcutaneous injection to mimic a physiologic insulin profile. Intravenous insulin is used in the acute inpatient setting for the management of hyperglycemic emergencies (eg, diabetic ketoacidosis).

Chronic Intermittent Insulin Therapy
Several forms of chronic intermittent insulin therapy, in which insulin is delivered intravenously or into the peritoneal space, have been evaluated.
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Chronic intermittent intravenous insulin therapy also referred to as outpatient intravenous insulin therapy, pulsatile intravenous insulin therapy, hepatic activation therapy, or metabolic activation therapy—involves delivering insulin intravenously over a 3-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. Chronic intermittent intravenous insulin therapy is principally designed to normalize the hepatic metabolism of glucose. In a 1993 article describing the development of the technique, Aoki et al 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 state: “We reasoned that if the liver of an IDDM [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 will 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 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 the purposes of CIIIT. Infusion pumps have received FDA marketing clearance through the 510(k) process. FDA determined that this device was substantially equivalent to existing devices for the delivery of intravenous medications. FDA product code: lZG.

**Centers for Medicare and Medicaid Services (CMS)**
In 2009, the Centers for Medicare and Medicaid Services issued a decision memo on use of outpatient intravenous insulin therapy, which stated:

“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, ie, 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 noncovered under Medicare when furnished pursuant to an OIVIT regimen.”

**Rationale/Source**
Following is a key summary of the literature to date, which primarily addresses whether CIIIT improves glycemic control in diabetic patients and whether CIIIT reduces end-organ damage associated with diabetes. Because of the many variables associated with management of diabetes, randomized controlled trials (RCTs) of CIIIT are necessary to permit conclusions about treatment effectiveness.

No studies were identified that investigate the proposed mechanism of action of CIIIT in humans.
CIIT and Glycemic Control in Diabetic Patients

In 1993, Aoki and colleagues published a case series of 20 patients with “brittle” type 1 diabetes. All patients received 4 daily injections of insulin (type of insulin not described); any 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 HbA1c 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 CIIT.

Aoki et al. also examined the effect of CIIT with hypertensive medications in 26 patients with type 1 diabetes and associated hypertension and nephropathy. 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 HbA1c levels of 7.4%. Patients also achieved acceptable baseline blood pressure control (below 140/90 mm Hg) with a variety of medications (i.e., angiotensin-converting enzyme [ACE] inhibitors, calcium channel blockers, loop diuretics, and alpha-2 agonists). While the study was randomized, it was not blinded in that sham CIIT procedures were not performed. Therefore, those patients receiving CIIT 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. Since all patients had adequate blood pressure control at baseline, the clinical significance of the decrease in antihypertensive dosage requirement associated with CIIT is uncertain.

Section Summary: CIIT and Glycemic Control in Diabetic Patients

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 HbA1c 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.

CIIT And Reductions In Diabetic End-Organ Damage

In 2010, Weinrauch et al published an RCT of the effects of CIIT on progression of nephropathy and retinopathy in 65 subjects with type 1 diabetes. Patients were randomized to standard therapy of 3 to 4 daily subcutaneous insulin injections (n=29; control group) or to standard therapy plus weekly CIIT (n=36; treatment group). Baseline demographic characteristics were similar between the 2 groups, as were age of onset, duration of diabetes, control of HbA1c levels, 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 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 smaller in the treatment group (0.09 mg/dL) than in the control group (0.39 mg/dL; p=0.035). While average creatinine clearance fell less in the treatment group (-5.1 mL/min), the difference versus standard therapy was not significant (-9.9 mL/min; p=0.30). Glycemic control did not vary significantly. The clinical significance of the difference in creatinine levels is unknown.
In 2000, Dailey et al reported on a prospective, multicenter, controlled study of the effects of CIIIT on the progression of diabetic nephropathy. They assessed 49 type 1 diabetes patients with nephropathy who were following the Diabetes Control and Complications Trial intensive therapy regimen. Of these, 26 were assigned to the control group, which continued intensive therapy, and 23 were assigned to the treatment group, which underwent weekly CIIIT plus intensive therapy. Both groups reported a significant decrease in HbA1c levels during the 18-month study period. Creatinine clearance declined in both groups as expected, but the rate of decline in the treatment group was significantly less than in the control group. The clinical significance of this finding is uncertain. Larger clinical trials that evaluate the end point of time to progression of renal failure are needed.

Section Summary: CIIIT and 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 postintervention, 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.

Ongoing Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
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<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>Unpublished</td>
<td>Multicenter Trial to Evaluate the Effects of Intensive Bolus Intravenous Insulin Delivery on Metabolic Integrity in Type 1 and Type 2 Diabetics Who Despite Tight Control and Proper Diet Still Suffer From Metabolic Problems</td>
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NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.

Summary of Evidence
For individuals who have type 1 diabetes who receive CIIIT, the evidence includes 2 RCTs and 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 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 studies is uncertain. Additionally, most published evidence appeared between 1993 and 2000 and, as a result, does not account for recent improvements in diabetes care. The evidence is insufficient to determine the effects of the technology on health outcomes.
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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.

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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.
Next Scheduled Review Date: 05/2018

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

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*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. 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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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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