BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Chronic Intermittent Intravenous Insulin Therapy (CIIIT)

Policy # 00015
Original Effective Date: 06/05/2002
Current Effective Date: 03/19/2014

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 (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.

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 non-insulin 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. 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, receive exogenous insulin therapy, with or without additional drug therapy with thiazolidinediones or metformin. Large-scale randomized studies have established that tight glucose control is associated with a decreased incidence of microvascular complications of diabetes (i.e., nephropathy, neuropathy, and retinopathy). Currently, the American Diabetics Association recommends a target hemoglobin A1c (HbA1c) concentration of less than 7%.

Chronic intermittent intravenous insulin therapy also referred to as outpatient intravenous insulin therapy (OIVIT), 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. 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 as they are delivered to the liver. It is hoped that this therapy ultimately results in improved glucose control through improved hepatic activation.

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Chronic intermittent intravenous insulin is typically delivered once weekly as outpatient therapy.

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, as they are determined to be substantially equivalent to predicate devices for the delivery of intravenous medications.

Centers for Medicare and Medicaid Services (CMS)
"Effective for claims with dates of service on and after December 23, 2009, the Centers for Medicare and Medicaid Services 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 OIVIT regimen are nationally non-covered under Medicare when furnished pursuant to an OIVIT regimen (see subsection A. above)."

Rationale/Source

Literature Review
This policy was originally created in 2002 and was regularly updated with literature searches. Following is a key summary of the literature to date:

Does CIIIT improve the hepatic metabolism of glucose?

Chronic intermittent intravenous insulin therapy is principally designed to normalize the hepatic metabolism of glucose. Although the exact physiologic mechanism is unclear, Aoki, one of the principal investigators of the technique, et al. proposed that in diabetic patients, lower levels of insulin in the portal vein are associated with a decreased concentration of the liver enzymes required for hepatic metabolism of glucose. Once weekly 6-hour intravenous pulsatile infusions of insulin while the patient ingests a carbohydrate meal are designed to increase the portal vein concentrations of insulin, ultimately stimulating the synthesis of glucokinase and other insulin-dependent enzymes. No studies were identified in the literature search that investigated the proposed scientific mechanism of CIIIT in humans.

Does CIIIT improve glycemic control in diabetic patients?

Because of the many variables associated with diabetic management, randomized controlled clinical trials are necessary to validate treatment effectiveness. A literature search did not identify any blinded randomized clinical trials focusing on the efficacy of CIIIT for glucose control.

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 CIIIT.

Aoki et al. also examined the effect of CIIIT 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 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. Since all patients had adequate blood pressure control at baseline, the clinical significance of the decrease in antihypertensive dosage requirement associated with CIIIT is uncertain.

Does CIIT reduce diabetic end-organ damage?

Because of the many variables associated with diabetic management, randomized controlled clinical trials are necessary to validate treatment effectiveness. A literature search identified two randomized clinical trials focusing on the efficacy of CIIIT for reducing diabetic end-organ complications.

In 2000, Dailey and colleagues reported on the effect of CIIIT on the progression of diabetic nephropathy. 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 HbA1c 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 to the control group. Again, the clinical significance of this finding is uncertain; larger clinical trials that look at the endpoint of time to progression of renal failure are needed.

In 2010, Weinrauch and colleagues published a study of the effects of CIIIT on progression of nephropathy and retinopathy in 65 subjects with type I diabetes. Patients were randomly allocated to standard therapy of 3-4 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/minute). Primary endpoints 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/minute vs. -9.9 mL/minute, respectively; p = 0.30). Glycemic control did not vary significantly. The clinical significance of the difference in creatinine levels is unknown and requires further evaluation in trials involving a larger number of patients.

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Ongoing Clinical Trials
A search of the online site ClinicalTrials.gov, in June 2013, found no clinical trials for this therapy. One related ongoing non-randomized, Phase III trial was identified. The "Effects of Intensive Bolus Intravenous Insulin Delivery on Metabolic Integrity in Type 1 and Type 2 Diabetes" trial is a multicenter trial to assess whether restoring metabolic integrity in 2,000 diabetic patients improves quality of life and complications associated with diabetes. (NCT01023165) This trial is expected to be completed in November 2015. In addition, a pilot (Canadian single-center) randomized controlled trial is being conducted in 148 patients to determine whether intermittent intensive insulin therapy is an effective therapeutic strategy that can preserve pancreatic beta-cell function and maintain glycemic control early in the course of type 2 diabetes. After a 3-week course of intensive insulin therapy, participants in the intervention arm will receive intermittent intensive insulin therapy for one week every 3 months for the duration of the trial (24 months); participants in the control arm will be treated with ongoing metformin monotherapy. The primary outcome measure will be baseline-adjusted beta-cell function at 2 years, measured by Insulin Secretion-Sensitivity Index-2 (ISSI-2). This trial is not yet open for participant recruitment, and is expected to be completed in December 2017. (NCT01755468)

Summary
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.

It is hypothesized that CIIIT improves hepatic glucose regulation. 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. However, the published studies are small and report benefits on intermediate outcomes only, i.e., changes in laboratory values. This evidence does not permit definitive conclusions regarding the health benefits of CIIIT. Therefore, the technique is considered investigational.

References

1. Blue Cross and Blu8 Shield Association, Medical Policy Reference Manual, "Chronic Intermittent Intravenous Insulin Therapy (CIIIT)" 2.01.43, 7:2013.
2. 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.
3. Aoki TT, Grecu EO, Arcangeli MA. Chronic intermittent intravenous insulin therapy corrects orthostatic hypotension of diabetes. Am J Med 1995; 99(6):683-4.
4. 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 1995; 18(9):1260-5.
5. 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.
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 2010.

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2013 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	No codes
HCPCS	A9277, E0784, G9147, J1817
ICD-9 Diagnosis	250.00 thru 250.93
ICD-9 Procedure	No codes

Policy History

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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.
Next Scheduled Review Date: 03/2015

*****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 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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