Healthy Blue

# Medical Policy

| | | | |
|---|---|---|---|
| **Subject:** | Hepatic Activation Therapy | | |
| **Document #:** | MED.00065 | **Publish Date:** | 12/16/2020 |
| **Status:** | Reviewed | **Last Review Date:** | 11/05/2020 |

## Description/Scope

This document addresses hepatic activation, also referred to as chronic intermittent intravenous insulin infusion therapy (CIIIT), outpatient intravenous insulin therapy (OIVIT), pulsatile intravenous insulin therapy (PIVIT), pulse insulin therapy (PIT) or metabolic activation therapy (MAT), which is a treatment of diabetes involving the delivery of insulin intravenously over a 5- to 7-hour period, in a pulsatile fashion, using a pump controlled by a computerized program. The dosages of insulin are adjusted, based on frequent blood glucose monitoring, and are designed to deliver a higher, more physiologic concentration of insulin to the liver than is delivered by traditional subcutaneous injections of insulin.

## Position Statement

**Investigational and Not Medically Necessary:**

Hepatic activation therapy is considered **investigational and not medically necessary** as a treatment of diabetes.

## Rationale

Individuals with type 1 diabetes require exogenous insulin therapy, with or without drug therapy with thiazolidinediones (to increase glucose uptake in the muscle, liver and gut) or metformin (to suppress hepatic glucose production). A variety of different types of exogenous insulin are also available, for instance, short, medium, and long acting preparations. Therefore, optimal management of type 1 diabetes requires an individualized regimen of dietary, drug, and insulin therapy, with the goal of a target HbA1c concentration of less than 7% to reduce microvascular and neuropathic complications of diabetes (American Diabetes Association, 2015). Because of the many variables associated with diabetic management, randomized controlled clinical trials are necessary to validate treatment effectiveness; in fact, drug therapies for diabetic management are routinely studied in randomized controlled trials.

Aoki and colleagues (1995) studied the effect of CIIIT on hypertensive medications in 26 subjects with type 1 diabetes and associated hypertension and nephropathy. The 26 participants 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 participants were being treated with 4 daily insulin injections and had achieved acceptable HbA1c levels of 7.4%. They also achieved acceptable baseline blood pressure control with a variety of medications. While the study was randomized, it was not blinded in that sham CIIIT procedures were not performed. Therefore, those receiving CIIIT received more intense follow-up during this period. During the treatment phase, participants

reported a significant decrease in the dosage of antihypertensive medicines. No difference in glycemic control was noted. Since all subjects had adequate blood pressure control at baseline, the clinical significance of the decrease in antihypertensive dosage requirement associated with CIIIT is uncertain.

Dailey and colleagues (2000) reported on the effect of CIIIT on the progression of diabetic nephropathy in a prospective, non-randomized trial of 49 individuals with type 1 diabetes. A total of 26 participants were assigned to the control group, while 23 individuals were assigned to the treatment group who underwent weekly CIIIT. Both groups reported a similar significant decrease in HbA1c levels 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 particularly since the decrease in HbA1c was similar in both groups.

In a pilot study (Weinrauch, 2007), 10 individuals were treated with PIVIT and compared to a control group with 8 individuals treated with subcutaneous insulin. The investigators hypothesized renal function would be preserved via mechanisms "involving cardiac autonomic function, cardiac mass, or efficiency or by hemostatic mechanisms." However, despite improvement of fuel oxidation noted by respiratory quotient, there was no significant difference between the control group and the treatment group in preservation of renal function.

In a randomized pilot study of PIVIT, Weinrauch (2010) reported the results of 65 evaluable participants out of 90 enrollees with type 1 diabetes and moderately severe (creatinine clearance greater than 30 mL/min; mean 58.2 mL/min PIVIT cohort and 63.5 mL/min control) nephropathy. All participants received standard therapy which included 3 to 4 insulin injections per day. Those randomized to the treatment group received additional weekly PIVIT with boluses of carbohydrates. Primary endpoints included decreased progression of diabetic renal disease and deterioration of the eye. During the follow-up period ranging from 6 to 22 months, the serum creatinine increased significantly from baseline in the control group (1.55 to 1.93; p=0.0038), but not in the PIVIT treatment group (1.62 to 1.71; p=0.1439). Although creatinine clearance decreased for both cohorts, the differences were not significant in the group receiving weekly PIVIT. Urine protein excretion did not significantly change at follow-up in either cohort. There were no statistically significant differences in the grade and occurrence of progressive retinopathy between the two groups. The authors concluded glycemia management was equally effective in both study groups and there was no beneficial retinal effect from PIVIT. Larger studies with longer follow-up are needed to further study the impact of PIVIT on renal preservation in type 1 diabetes.

All other studies of CIIIT therapy were case series. Additionally, hepatic activation therapy is not discussed as a treatment option in the clinical practice recommendations of the American Diabetes Association (ADA). In the 2018 ADA Standards of Medical Care in Diabetes, recommendations for diabetes treatment include multiple dose insulin injections (basal and prandial insulin) or continuous subcutaneous insulin therapy.

There have been several studies that suggest CIIIT may improve glycemic control, slow progression of nephropathy or facilitate blood pressure control. However, the limited number of published studies lack adequate controls, randomization, and blinding, and the small sample sizes of the available studies preclude definitive conclusions regarding the health benefit of CIIIT.

In 2009, Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Determination (NCD) noting that "OIVIT does not improve health outcomes."

## Background/Overview

Hepatic activation, also referred to as CIIIT, PIVIT, or MAT, is a proposed treatment of diabetes, involving the delivery of insulin intravenously over a 5- to 7-hour period in a pulsatile fashion, using a pump controlled by a computerized program. The dosages of insulin are adjusted, based on frequent blood glucose monitoring, and are designed to deliver a higher, more physiologic concentration of insulin to the liver than is delivered by traditional subcutaneous injections of insulin. It is hoped that this therapy ultimately results in improved glucose control through improved hepatic activation. Although the exact physiologic mechanism is unclear, Aoki, one of the principal investigators of MAT, proposes that, in diabetics, lower levels of insulin in the portal vein are associated with a decreased concentration of the liver enzymes required for hepatic metabolism of glucose. Weekly 5- to 7-hour intravenous pulsatile infusions of insulin while the individual 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.

## Definitions

Diabetes mellitus: A variable disorder of carbohydrate metabolism caused by a combination of hereditary and environmental factors and usually characterized by inadequate secretion or utilization of insulin, by excessive urine production, by excessive amounts of sugar in the blood and urine, and by thirst, hunger, and loss of weight.

Insulin: A protein hormone that is synthesized in the pancreas from proinsulin and secreted by the beta cells of the islets of Langerhans, that is essential for the metabolism of carbohydrates, lipids, and proteins, that regulates blood sugar levels by facilitating the uptake of glucose into tissues, by promoting its conversion into glycogen, fatty acids, and triglycerides, and by reducing the release of glucose from the liver, and that when produced in insufficient quantities results in diabetes mellitus.

## Coding

*The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

**When Services are Investigational and Not Medically Necessary:**
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

**HCPCS**

| | |
|---|---|
| G9147 | Outpatient intravenous insulin treatment (OIVIT) either pulsatile or continuous, by any means, guided by the results of measurements for: respiratory quotient; and/or, urine urea nitrogen (UUN); and/or, arterial, venous or capillary glucose; and/or potassium concentration |

**ICD-10 Diagnosis**

All diagnoses

## References

**Peer Reviewed Publications:**

1. Aoki TT, Benbarka MM, Okimura MC, et al. Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus. Lancet. 1993; 342(8870):515-518.
2. Aoki TT, Grecu EO, Arcangeli MA. Chronic intermittent intravenous insulin therapy corrects orthostatic hypotension of diabetes. Am J Med. 1995; 99(6):683-684.
3. Aoki TT, Grecu EO, Arcangeli MA, et al. Chronic intermittent intravenous insulin therapy: a new frontier in diabetes therapy. Diabetes Technol Ther. 2001; 3(1):111-123.
4. Aoki TT, Grecu EO, Prendergast JJ, et al. Effect of chronic intermittent intravenous insulin therapy on antihypertensive medication requirement in IDDM subjects with hypertension and nephropathy. Diabetes Care.1995; 18(9):1260-1265.
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):1491-1495.
6. Gill G, Williams G. Long term intermittent intravenous therapy and type 1 diabetes mellitus. Lancet.1993; 342(8878):1056-1058.
7. Weinrauch LA, Burger AJ, Aepfelbacher F, et al. A pilot study to test the effect of pulsatile insulin infusion on cardiovascular mechanisms that might contribute to attenuation of renal compromise in type 1 diabetes mellitus patients with proteinuria. Metabolism. 2007; 56(11):1453-1457.
8. Weinrauch L, Sun J, Gleason RE, et al. Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 diabetes mellitus. Metabolism 2010; 59(10):1429-1434.

**Government Agency, Medical Society, and Other Authoritative Publications:**

1. American Diabetes Association. Standards of Medical Care in Diabetes-2018: Summary of Revisions. Diabetes Care. 2018; 41 Suppl 1:S4-S6.
2. Centers for Medicare and Medicaid Services (CMS). National Coverage Determination: Outpatient intravenous insulin treatment (40.7). Effective December 23, 2009. Available at: http://www.cms.gov/mcd/index_list.asp?list_type=ncd. Accessed on September 15, 2020.
3. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and American college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015; 21 Suppl 1:1-87.
4. Powers MA, Bardsley J, Cypress M, et al. American Diabetes Association. Diabetes Self-management Education and Support in Type 2 Diabetes: A Joint Position Statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. July 2015.

Available at: https://care.diabetesjournals.org/content/early/2015/06/02/dc15-0730. Accessed on September 15, 2020.

## Websites for Additional Information

1. American Diabetes Association. Available at: http://www.diabetes.org/. Accessed on September 15, 2020.
2. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Diabetes. Available at https://www.niddk.nih.gov/health-information/diabetes. Accessed on September 15, 2020.

## Index



## Document History

| Status | Date | Action |
|---|---|---|
| Reviewed | 11/05/2020 | Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References and Websites sections. |
| Reviewed | 11/07/2019 | MPTAC review. Updated References and Websites sections. |
| Reviewed | 01/24/2019 | MPTAC review. Updated Rationale, References, and Websites sections. |
| Reviewed | 02/27/2018 | MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale, Background/Overview, References, and Websites sections. |
| Reviewed | 02/02/2017 | MPTAC review. Updated References and Websites sections. |
| Reviewed | 02/04/2016 | MPTAC review. Updated Background/Overview, References and Websites sections. Removed ICD-9 codes from Coding section. |
| Reviewed | 02/05/2015 | MPTAC review. Updated References and Websites sections. |
| Reviewed | 02/13/2014 | MPTAC review. Updated References and Websites sections. |
| Reviewed | 02/14/2013 | MPTAC review. Updated References and Websites sections. |
| Reviewed | 02/16/2012 | MPTAC review. Updated References and Websites sections. |
| Reviewed | 02/17/2011 | MPTAC review. Updated References and Websites sections. |
| Reviewed | 08/19/2010 | MPTAC review. Updated Rationale, References and Websites sections. |
| | 04/01/2010 | Updated Coding section with 04/01/2010 HCPCS changes. |
| Reviewed | 08/27/2009 | MPTAC review. Updated References and Websites sections. |
| Reviewed | 08/28/2008 | MPTAC review. References and websites updated. Updated Coding section with 10/01/2008 ICD-9 changes. |

| | | |
|---|---|---|
| | 02/21/2008 | The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting. |
| Reviewed | 08/23/2007 | MPTAC review. References and Websites sections updated. |
| Reviewed | 09/14/2006 | MPTAC review. References section updated. |
| Revised | 09/22/2005 | MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization. |

| **Pre-Merger Organizations** | **Last Review Date** | **Document Number** | **Title** |
|---|---|---|---|
| Anthem, Inc. | | No prior document | |
| WellPoint Health Networks, Inc. | 09/23/2004 | 2.01.06 | Hepatic Activation Therapy (CIIIT/PIVIT) |