SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

Note:

This policy does not apply to patients under the age of 2, for whom integrated insulin infusion and glucose monitoring systems may be considered medically necessary and covered.

Coverage Criteria

I. An integrated insulin infusion and glucose monitoring system may be considered medically necessary and covered for the treatment of insulin-dependent diabetes when all of the following criteria (A. - D.) are met:
A. The requested device is FDA-approved and is being used in accordance with the approved indications of use (see Table 1 for list of devices and indications); and

B. The patient has completed a comprehensive diabetes education program; and

C. The patient has a documented history of inadequate glycemic control despite both of the following (1.-2.):
   1. Multiple daily injections; and
   2. A medically necessary continuous glucose monitor (CGM) for at least 3 months prior to the initiation of the integrated system (Note: In rare instances, simultaneous placement on an insulin infusion pump and glucose monitoring system may be necessary); and

D. Clinical records document either of the following (1.-2.):
   1. Recurring episodes (two or more events within a 30 day period) of clinically significant hypoglycemia, including suspected episodes (e.g., nocturnal); or
   2. Impaired awareness or the inability to communicate hypoglycemia.

II. An integrated insulin infusion and glucose monitoring system is considered investigational and not covered when the above criterion I. is not met, including but not limited to any of the following (A.-C.):

   Note: This policy does not apply to patients under the age of 2 year for whom artificial pancreas devices and other integrated systems may be considered medically necessary and covered.

   A. The device is not FDA-approved or is being used outside of the FDA-approved indications; or
   B. Non-insulin dependent children or adults; or
   C. Individuals with gestational diabetes mellitus (GDM)

Replacement of Integrated Insulin Infusion and Glucose Monitoring System

III. Replacement of an existing integrated insulin infusion and glucose monitoring system may be considered medically necessary and covered when documentation that one or more of the following device components meet all of the following criteria (A.-C.):

   A. Are no longer functional; and
   B. Are not under warranty; and
   C. Cannot be repaired.

IV. Replacement of an existing integrated insulin infusion and glucose monitoring system is considered not medically necessary and not covered when criterion III. above is not met.
V. An upgrade from functioning devices which are able to effectively control glycemia is considered not medically necessary and not covered.

Enhancements/Optional Accessories

VI. Enhancements or optional accessories for integrated systems via smartphones, tablets and computers are considered convenience items and therefore are not medically necessary and are not covered, including, but not limited to:

A. Mobile Apps (e.g., Dexcom G5 Mobile App, Dexcom Share2 App, Dexcom Follow, Dexcom CLARITY® Reports App, MiniMed Connect, t:connect®)
B. Diabetes management software (e.g., Dexcom CLARITY®, FreeStyle CoPilot Health Management System, Medtronic CareLink® system)
C. Remote glucose monitoring devices (e.g., mySentry)

BILLING GUIDELINES

- Although insulin pumps do not require prior authorization when billed individually for Type 1 diabetes, prior authorization is expected when pumps are billed as part of an integrated system with a continuous glucose monitor.

- Code A4224 may not be billed more than 52 times per calendar year.

CPT/HCPCS CODES

<table>
<thead>
<tr>
<th>All Lines of Business Except Medicare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Authorization Required</td>
</tr>
<tr>
<td>A9274</td>
</tr>
<tr>
<td>A9276</td>
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<tr>
<td>A9277</td>
</tr>
<tr>
<td>A9278</td>
</tr>
<tr>
<td>K0553</td>
</tr>
</tbody>
</table>
### MEDICAL POLICY

**Diabetes: Integrated Insulin Infusion and Glucose Monitoring Systems**  
*(All Lines of Business Except Medicare)*

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>K0554</td>
<td>Receiver (monitor), dedicated, for use with therapeutic continuous glucose monitor system</td>
</tr>
<tr>
<td>E0784</td>
<td>External ambulatory infusion pump, insulin</td>
</tr>
<tr>
<td>E0787</td>
<td>External ambulatory infusion pump, insulin, dosage rate adjustment using therapeutic continuous glucose sensing</td>
</tr>
<tr>
<td>S1034</td>
<td>Artificial pancreas device system (eg, low glucose suspend [LGS] feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices</td>
</tr>
<tr>
<td>S1035</td>
<td>Sensor; invasive (eg, subcutaneous), disposable, for use with artificial pancreas device system</td>
</tr>
<tr>
<td>S1036</td>
<td>Transmitter; external, for use with artificial pancreas device system</td>
</tr>
<tr>
<td>S1037</td>
<td>Receiver (monitor); external, for use with artificial pancreas device system</td>
</tr>
</tbody>
</table>

#### No Prior Authorization Required

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>A4224</td>
<td>Supplies for maintenance of insulin infusion catheter, per week</td>
</tr>
<tr>
<td>A4225</td>
<td>Supplies for external insulin infusion pump, syringe type cartridge, sterile, each</td>
</tr>
<tr>
<td>A4230</td>
<td>Infusion set for external insulin pump, non needle cannula type</td>
</tr>
<tr>
<td>A4231</td>
<td>Infusion set for external insulin pump, needle type</td>
</tr>
<tr>
<td>A4232</td>
<td>Syringe with needle for external insulin pump, sterile, 3 cc</td>
</tr>
<tr>
<td>J1817</td>
<td>Insulin for administration through DME (i.e., insulin pump) per 50 units</td>
</tr>
<tr>
<td>K0601</td>
<td>Replacement battery for external infusion pump owned by patient, silver oxide, 1.5 volt, each</td>
</tr>
<tr>
<td>K0602</td>
<td>Replacement battery for external infusion pump owned by patient, silver oxide, 3 volt, each</td>
</tr>
<tr>
<td>K0603</td>
<td>Replacement battery for external infusion pump owned by patient, alkaline, 1.5 volt, each</td>
</tr>
<tr>
<td>K0604</td>
<td>Replacement battery for external infusion pump owned by patient, lithium, 3.6 volt, each</td>
</tr>
<tr>
<td>K0605</td>
<td>Replacement battery for external infusion pump owned by patient, lithium, 4.5 volt, each</td>
</tr>
</tbody>
</table>

#### Unlisted Codes

All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then **prior-authorization is required.**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1399</td>
<td>Durable medical equipment, miscellaneous</td>
</tr>
</tbody>
</table>

**DESCRIPTION**

**Combination Integrated Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM) Systems**
This is the general term for a system that allows for communication between two devices:

1. an insulin pump that administers continuous subcutaneous insulin infusion (CSII), and
2. a continuous glucose monitor (CGM)

These systems are also known as CSII-CGM systems, or combination systems. There are several types of integrated systems, all with varying levels of automation. These systems may or may not include software for tracking and trending glucose readings. Some systems connect the insulin pump to the CGM using wired technology while others are wireless. These CSII-CGM systems include sensor-augmented systems and artificial pancreas device systems, and are described in detail below. Please see Table.1 below for a list of FDA-approved integrated CSII-CGM devices.

## Sensor-Augmented Systems

In these systems, the CGM sensor communicates glucose readings to the pump via a transmitter. This transmitter allows patients to view real-time glucose values, and will not use the continuous glucose monitoring (CGM) data to calculate insulin doses. Patients are still required to perform self-monitoring of blood glucose by way of a finger stick to generate the information needed to adjust insulin levels. These systems typically require manual adjustment of insulin administration rates as well as manual calculation and administration of pre-meal insulin bolus doses.

## Artificial Pancreas Device System (APDS)

According to the U.S. Food & Drug Administration (FDA):

“The Artificial Pancreas Device System is a system of devices that closely mimics the glucose regulating function of a healthy pancreas. Sometimes an artificial pancreas device system is referred to as a "closed-loop" system, an ‘automated insulin delivery’ system, or an ‘autonomous system for glycemic control.’

Most Artificial Pancreas Device Systems consists of three types of devices already familiar to many people with diabetes:

1. **Continuous Glucose Monitor (CGM).** A sensor placed under the patient’s skin (subcutaneously) measures the glucose in the fluid around the cells (interstitial fluid) which is associated with blood glucose levels. A small transmitter sends information to a receiver.
   - **Blood Glucose Device (BGD).** Currently, to get the most accurate estimates of blood glucose possible from a CGM, the patient needs to periodically calibrate the CGM using a blood glucose measurement from a BGD.
2. **Control algorithm.** A control algorithm is software embedded in an external processor (controller) that receives information from the CGM and performs a series of mathematical calculations. Based on these calculations, the controller sends dosing instructions to the
infusion pump. The control algorithm can be run on any number of devices including an insulin pump, computer or cellular phone. The FDA does not require the control algorithm to reside on the insulin pump.

3. **Insulin pump.** Based on the instructions sent by the controller, an infusion pump adjusts the insulin delivery to the tissue under the skin.

An Artificial Pancreas Device System not only monitors glucose levels in the body but also automatically adjusts the delivery of insulin to reduce high blood glucose levels (hyperglycemia) and minimize the incidence of low blood glucose (hypoglycemia) with little or no input from the patient.”

**Types of Artificial Pancreas Device Systems (APDS)**

According to the FDA:

“All researchers and manufacturers are developing three main categories of Artificial Pancreas Delivery Systems. They differ in how the insulin pump acts on readings from the continuous glucose monitoring system.

- **Threshold Suspend Device System**

The goal of a threshold suspend device system is to help reverse a dangerous drop in blood glucose level (hypoglycemia) or reduce its severity by temporarily suspending insulin delivery when the glucose level falls to or approaches a low glucose threshold. These are sometimes referred to as “low glucose suspend systems.”

This kind of system serves as a potential back-up when a patient is unable to respond to a low blood sugar (hypoglycemic) event. Patients using this system will still need to be active in managing their blood glucose levels by periodically checking their blood glucose levels and by administering insulin or eating.

- **Insulin-Only System**

An insulin-only system achieves a target glucose level by automatically increasing or decreasing the amount of insulin infused based on the CGM values. These systems may be hybrid systems that automatically adjust basal insulin with the user manually delivering bolus insulin to cover meals, or could be fully closed loop systems, where the system automatically adjusts basal insulin and provide insulin for meals.

- **Bi-Hormonal Control System**

A bi-hormonal control system achieves a target glucose level by using two algorithms to instruct an infusion pump to deliver two different hormones – one hormone (insulin) to lower glucose
levels and another (such as glucagon) to increase blood glucose levels. The bi-hormonal system mimics the glucose-regulating function of a healthy pancreas more closely than an insulin-only system.”

Table 1. Examples of FDA-Approved Integrated Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM) Systems Currently On the Market

<table>
<thead>
<tr>
<th>Device</th>
<th>Indications/Contraindications</th>
<th>Age</th>
</tr>
</thead>
</table>
| **MiniMed Paradigm® REAL-Time Revel™ System**<br>By Medtronic | • Indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin.  
• Use of insulin pumps with the optional sensor and transmitter components is indicated for continuous or periodic monitoring of glucose levels in the fluid under the skin, and possible low and high blood glucose episodes in adults (ages 18 and older). | ≥ 18 years |
| **t:slim G4™**<br>By Tandem® Diabetes Care | • Intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The t:slim G4 Insulin Pump can be used solely for continuous insulin delivery and as part of the t:slim G4 System to receive and display continuous glucose measurements from the Dexcom G4 Platinum Sensor and Transmitter.  
• The t:slim G4 System also includes continuous glucose monitoring (CGM) indicated for detecting trends and tracking patterns in persons with diabetes for use as an adjunctive device to complement, not replace, information obtained from standard home glucose monitoring devices.  
• The t:slim G4 System is indicated for use in individuals 12 years of age and greater  
• The t:slim G4 System is intended for single patient use and requires a prescription | ≥ 12 years |
<p>| <strong>t:slim X2™ Insulin Pump</strong> | • Intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. | ≥ 6 years  |</p>
<table>
<thead>
<tr>
<th>MEDICAL POLICY</th>
<th>Diabetes: Integrated Insulin Infusion and Glucose Monitoring Systems (All Lines of Business Except Medicare)</th>
</tr>
</thead>
</table>
| **By Tandem® Diabetes Care** | insulin. The t:slim X2 Insulin Pump can be used solely for continuous insulin delivery and as part of the t:slim X2 System to receive and display continuous glucose measurements from the Dexcom G5 Mobile Sensor and Transmitter.  
- The t:slim X2 System also includes continuous glucose monitoring (CGM) indicated for the management of diabetes. The Dexcom G5 Mobile CGM is designed to replace fingerstick blood glucose testing for diabetes treatment decisions.  
- The t:slim X2 System is indicated for use in individuals 6 years of age and greater.  
- The t:slim X2 System is intended for single patient use and requires a prescription. The device is indicated for use with NovoLog or Humalog U-100 insulin. |
| **t:slim X2™ Insulin Pump with Control-IQ** By Tandem® Diabetes Care | • Intended for single patient, home use and requires a prescription. The pump is indicated for use with NovoLog or Humalog U-100 insulin.  
• Control-IQ technology is intended for use with a compatible integrated continuous glucose monitor (iCGM, sold separately) and ACE pump to automatically increase, decrease, and suspend delivery of basal insulin based on CGM readings and predicted glucose values. It can also deliver correction boluses when the glucose value is predicted to exceed a predefined threshold.  
• Control-IQ technology is intended for the management of Type 1 diabetes mellitus in persons 14 years of age and greater. Control-IQ technology is intended for single patient use. Control-IQ technology is indicated for use with NovoLog or Humalog U-100 insulin.  
• Control-IQ technology should not be used by anyone under the age of six years old. It should also not be used in patients who require less than 10 units of insulin per day or who weigh less than 55 pounds.  
• Control-IQ technology is not indicated for use in pregnant women, persons on dialysis, or critically ill patients.  
• The pump is not intended for anyone unable or unwilling to:  
  o Use the pump, CGM, and all other system components in accordance with their respective instructions for use  
  o Test BG levels as recommended by a healthcare provider  
  o Demonstrate adequate carbohydrate-counting skills  
  o Maintain sufficient diabetes selfcare skills  
  o See a healthcare provider(s) regularly |
<p>| <strong>MiniMed 530G</strong> By Medtronic | • Intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of diabetes in persons requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin...can be programmed to automatically... |</p>
<table>
<thead>
<tr>
<th>MEDICAL POLICY</th>
<th>Diabetes: Integrated Insulin Infusion and Glucose Monitoring Systems (All Lines of Business Except Medicare)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>suspend delivery of insulin when the sensor glucose value falls below a predefined threshold value.</td>
</tr>
<tr>
<td></td>
<td>• Not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on values provided by the MiniMed 530G System</td>
</tr>
<tr>
<td></td>
<td>• Not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the Threshold Suspend alarm to take measures to prevent or treat hypoglycemia themselves.</td>
</tr>
<tr>
<td><strong>MiniMed 630G</strong>&lt;br&gt;By Medtronic</td>
<td>• Intended for continuous delivery of basal insulin (at user selected rates) and administration of insulin boluses in for the management of diabetes mellitus in persons fourteen years of age and older requiring insulin, as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 630G system includes SmartGuard, which can be programmed to temporarily suspend delivery of insulin for up to two hours when the sensor glucose value falls below a predefined threshold value.</td>
</tr>
<tr>
<td></td>
<td>• Not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on values provided by the MiniMed 630G system.</td>
</tr>
<tr>
<td></td>
<td>• Not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to... take measure to prevent or treat hypoglycemia themselves.</td>
</tr>
<tr>
<td><strong>MiniMed 670G</strong>&lt;br&gt;By Medtronic</td>
<td>• Intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of Type 1 diabetes mellitus in persons, seven years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin.</td>
</tr>
<tr>
<td></td>
<td>• Not intended for use in children under the age of 7.</td>
</tr>
<tr>
<td></td>
<td>• Not intended for use in patients who require less than a total daily insulin dose of 8 units per day.</td>
</tr>
<tr>
<td></td>
<td>• The reservoir is contraindicated for the infusion of blood or blood products.</td>
</tr>
<tr>
<td></td>
<td>• Infusion sets are indicated for subcutaneous use only and not for intravenous (IV) infusion or the infusion of blood or blood products.</td>
</tr>
</tbody>
</table>
REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of integrated continuous subcutaneous insulin infusion (CSII) and continuous glucose monitor (CGM) (CSII-CGM) systems, including artificial pancreas device systems, as a treatment for diabetes mellitus. Below is a summary of the available evidence identified through January of 2020.

Of note, the European equivalent of the MiniMed 530G is the MiniMed Paradigm® Veo. The Veo has a wider glucose range to trigger suspension (40–110 mg/dL), a higher maximum bolus capacity (75 units vs. 25 units) and automatically recalibrates following suspension whereas the 530G asks the user if they want to recalibrate. The differences are due to FDA requirements. The software for the Threshold Suspend tool is the same for the 530G System and the Veo. Although the sensors for the two pumps are not identical, they operate using similar principles and fundamental scientific technology. Therefore, studies evaluating the Veo are applicable to the 530G.

Artificial Pancreas Device Systems

Three recent systematic reviews evaluated the efficacy of artificial pancreas device systems relative to conventional pump therapy and other types of insulin-based treatment. Reviews reported improvements in patients’ time spent in the hypoglycemic phase, proportion of time with sensor glucose level above 10 mmol/L and patients’ daily insulin requirements. Each study concluded that artificial pancreas systems are safe and efficacious approaches for the treatment of type 1 diabetes, despite the need for additional studies to further establish validity.

Sensor-Augmented CSII-CGM Systems

Systematic Reviews and Technology Assessments

In 2016, the United Kingdom-based National Institute for Health Research (NHS) published a systematic review and technology assessment integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm Veo system and the Animas Vibe and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes. This technology assessment informed the 2016 guidelines published by the National Institute for Health and Care Excellence (NICE) on these devices (see Clinical Practice Guidelines section below). The review of the evidence was performed prior to March 2015. In the evaluation of the clinical effectiveness of the integrated continuous subcutaneous insulin infusion (CSII)-CGM system (Animas Vibe pump with Decom G4 CGM), seven comparative studies were included. Three of the included studies compared CSII-CGM to CSII-SMBG (self-monitoring of blood glucose), and four studies compared CSII-CGM to multiple daily injections (MDI)-SMBG. While most of these studies included small sample sizes (n=16 to 76), the large RCTs included in the review are described in detail below. Although the review reported that the integrated CSII-CGM system significantly improved HbA1c levels and quality of life compared to MDI-SMBG, the evidence base was poor and the quality of the included studies deemed as low.
Randomized Controlled Trials

In 2008, Hirsch et al. published six-month results of a multicenter RCT designed to evaluate the effectiveness and safety of the Paradigm CSII-CGM system compared with a Paradigm CSII pump used with SMBG (CSII-SMBG), including 146 subjects (ages of 12 to 72 years) with type 1 diabetes and baseline HbA1c levels of greater than or equal to 7.5%. At six months, change in HbA1c from baseline was significant for both groups (p<0.001), however; the between-group differences were not significant (CSII-CGM group = -0.71% [+/-0.71%] and by -0.56 [+/-0.72%] in the CSII-SMBG group). In addition, the percentage of subjects that achieved 7% HbA1c was not significantly different between groups. CSII-CGM subjects showed no change in mean hypoglycemia area under the curve (AUC), whereas CSII-SMBG subjects showed an increase (p=0.001) in hypoglycemia AUC during the blinded periods of the study. The between-group difference in hypoglycemia area under the curve (AUC) was significant (p<0.0002). Fourteen severe hypoglycemic events occurred (11 in the CSII-CGM group and three in the CSII-SMBG group, p=0.04). One limitation of this study was the enrollment of subjects who were not actively engaged in their diabetes self-management prior to the study.

In 2010, Bergenstal et al. published one-year results from a multicenter RCT evaluating the effectiveness of sensor-augmented insulin pump therapy in type 1 diabetes. Efficacy of Paradigm REAL-Time sensor-augmented pump therapy (CSII-CGM) was compared with that of a regimen of MDI-SMBG in 485 patients (329 adults and 156 children) with inadequately controlled type 1 diabetes. At one year, the baseline mean HbA1c had decreased from 8.3% to 7.5% in the CSII-CGM group, compared to the MDI-SMBG group, where the decrease was from 8.3% to 8.1%. The difference in decrease in HbA1c was significantly different between the two groups (p<0.001). The proportion of patients who reached the glycated hemoglobin target (<7%) was greater in the CSII-CGM group than in the MDI-SMBG group. The rate of severe hypoglycemia in the CSII-CGM group (13.31 cases per 100 person-years) did not differ significantly from that in the MDI-SMBG group (13.48 per 100 person-years, p=0.58). Limitations of this trial include lack a blinding of patients, investigators, and caregivers with regards to the intervention used; limited generalizability of results due to narrow range of HbA1c used as inclusion criteria; and patients in the CSII-CGM group received more contact with clinical staff members than did patients in the MDI-SMBG group during the first 5 weeks of the study.

In 2012, Battelino et al. published findings of a European multicenter crossover trial that included 153 children and adults with type 1 diabetes. The study used the MiniMed Paradigm REAL-Time system, which integrates a CGM device and an insulin pump system. Patients were randomized to use of the system for 6 months with the sensor on and 6 months with the sensor off, in random order, with a washout period of 4 months between interventions. Baseline HbA1c ranged from 7.5% to 9.5%. After treatment, mean HbA1c was 8.04% in the sensor on arm and 8.47% in the sensor off arm. The mean difference in HbA1c between groups was -0.43% (95% CI, -0.32% to -0.55%; p<0.001). Neither of the above trials were blinded, and neither compared continuous with intermittent use of the CGM.

Nonrandomized Studies
In 2013, Nørgaard et al. reported on the largest and longest multicenter prospective observational study of continuous glucose monitoring with insulin infusion pumps, so called sensor-augmented pump therapy. The investigators reported on a 12-month observational study in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII), upon the introduction of continuous glucose monitoring (CGM). The study was conducted in 15 countries to document the real-life use of sensor-augmented pump therapy and assess which variables are associated with improvement in type 1 diabetes management. Data from 263 patients (38% male; mean age, 28.0±15.7 years [range, 1-69 years]; body mass index, 23.3±4.9 kg/m(2); diabetes duration, 13.9±10.7 years; CSII duration, 2.6±3 years) were collected. Baseline mean HbA1c was 8.1±1.4%; 82% had suboptimal HbA1c (≥7%). The investigators found that the average sensor use for 12 months was only 30% (range, 0-94%), and that sensor use decreased with time (first 3 months, 37%; last 3 months, 27%). The investigators found that there were significantly more patients with an HbA1c value of < 7.5% after 3 months of sensor-augmented pump therapy than at baseline (baseline, 29%; 3 months, 37%) However, the percentage of patients with an HbA1c value of < 7.5% decreased over the 12-month observation period, such that the percentage of patients with an HbA1c value of < 7.5% after 12 months was not statistically significantly higher than at baseline.

APD Systems with Threshold Suspend

Systematic Reviews and Technology Assessments

In 2016, the ECRI Institute published an updated emerging technology report on threshold suspend systems for managing hypoglycemia in patients with type 1 diabetes. This report included two RCTs (described below), one small prospective pre-post study in 21 children, and one retrospective analysis (described below). All four studies reported on the number of moderate and/or severe hypoglycemia events. Although studies reported this measure in different ways, study patients using the MiniMed Veo or 530G with the threshold suspend/LGS feature activated had improvement in this outcome compared with study patients using sensor-augmented pump therapy, the MiniMed Veo or 530G with the threshold-suspend/LGS feature turned off, or patients using a standard insulin pump alone. The report concluded that compared with sensor-augmented systems therapy alone, sensor-augmented integrated systems with threshold suspend resulted in fewer severe hypoglycemic episodes (requiring assistance for treatment or resulting in seizure or coma), including nocturnal episodes. The assessment deemed the strength of evidence for this outcome as moderate. However, conclusions could not be reached regarding the following outcomes due to low or very low strength of evidence: whether threshold suspend devices were more effective than standard pump therapy alone for any outcomes reported, including severe hypoglycemic episodes, HbA1c and ketoacidosis. In addition, although the report indicated that the threshold suspend systems did not appear to be more effective than sensor-augmented systems, or standard pumps, this was based on low level evidence (only two RCTs).

In the 2016 NHS systematic review of integrated sensor-augmented pump therapy systems described above, the reviewers reported that the Veo system reduced the number of hypoglycemic events compared to other treatments, but did not improve other outcomes, including HbA1c levels. This analysis was based on two RCTs, one of which compared Veo with an integrated CSII-CGM system and
the other study compared Veo with a CSII-SMBG system in a mixed population. These two RCTs are described in detail below.\textsuperscript{9,10} The reviewers deemed the evidence base as poor for all treatments, including the Veo, with the quality of the included studies being generally low.

**Randomized Controlled Trials (RCTs)**

In 2012, Garg et al. published data from the in-clinic arm of the ASPIRE randomized crossover trial that included 50 patients with type 1 diabetes who had at least 3 months’ experience with an insulin pump system.\textsuperscript{11} The goal of the study was to evaluate whether the severity and duration of hypoglycemia was reduced when the LGS feature was used. After a 2-week run-in period, patients underwent two in-clinic exercise sessions to induce hypoglycemia. The LGS feature on the insulin pump was turned on in one session and off in the other session, in random order. The study protocol called for patients to start exercise with a glucose level of 100 to 140 mg/dL, and to use a treadmill or stationary bicycle until their plasma glucose level was 85 mg/dL or less. The mean duration of hypoglycemia was significantly less during the LGS-on sessions (138.5 minutes; SD=68 minutes) than the LGS-off sessions (170.7 minutes; SD=91 minutes; \(p=0.006\)). In addition, hypoglycemia severity was significantly lower in the LGS-on group, with the mean lowest glucose level being 59.5 mg/dL in the LGS-on group and 57.6 mg/dL (\(p=0.015\)) in the LGS-off group.

In 2013, Bergenstal et al. published the results of the ASPIRE RCT that evaluated the efficacy and safety of sensor-augmented insulin-pump therapy with and without the threshold suspend feature in patients with nocturnal hypoglycemia, using the European-approved version of the MiniMed 530G, called the Paradigm Veo System.\textsuperscript{9} Patients with type 1 diabetes and documented nocturnal hypoglycemia were randomly assigned to receive sensor-augmented insulin-pump therapy with or without the threshold suspend feature for three months. Of a total of 247 patients, 127 patients were randomly assigned to receive sensor-augmented insulin-pump therapy with the threshold suspend and 126 patients served as controls, receiving standard sensor-augmented insulin-pump therapy. The changes in HbA1c values were similar in the two groups. However, the mean AUC for nocturnal hypoglycemic events that was 37.5% lower in the threshold suspend group than in the control group (980 ± 1200 mg per deciliter \(\times\) minutes versus 1568 ± 1995 mg per deciliter \(\times\) minutes; \(p<0.001\)). Thus, hypoglycemic events occurred 31.8% less frequently in the threshold suspend group than in the control group (1.5 ± 1.0 vs. 2.2 ± 1.3 per patient-week, \(p<0.001\)). The authors concluded that over a three month period, the use of sensor-augmented insulin-pump therapy with the threshold suspend feature reduced nocturnal hypoglycemia without increasing glycated hemoglobin values.

In 2013, Ly et al. also published results from an RCT that included 95 subjects randomized to six months of treatment with either Medtronic Paradigm Veo System \((n=46)\) or to insulin pump treatment alone \((n=49)\).\textsuperscript{10} Subjects were aged 4 to 50 years old with type 1 diabetes, had used an insulin pump for at least 6 months, had an HbA1c level of 8.5% or less, and had impaired awareness of hypoglycemia. The authors noted that the baseline rate of severe hypoglycemic events (defined as hypoglycemic seizure or coma) and moderate hypoglycemic events (defined as an event requiring assistance from another person) was significantly higher in the Veo group (129.6 vs 20.7 events per 100 subject-months). After six months, the frequency of moderate to severe hypoglycemic events per 100 subject-months was 34.2
in the control group vs. 9.6 in the Veo group. The authors reported the incidence rate ratio was 3.6 (p<0.001), indicating greater improvement in the LGS group compared with the pump-only group. The incidence rate ratio for moderate and severe events excluding the two children was 1.7 (p=0.08). Mean HbA1c level, a secondary outcome, did not differ between groups at baseline or at six months. Change in HbA1c levels during the treatment period was -0.06% in the control group and -0.1% in the experimental group.

**Nonrandomized Studies**

In 2015, Agrawal et al. published a retrospective study of the Medtronic Paradigm Veo System, including 20,973 subjects who were allowed to adjust the threshold suspend feature manually and upload their pump and sensor data for a period of 40 weeks. The authors compared data from 758,382 subject-days when the suspend feature was activated to the 166,791 subject-days when it was not. Overall 70% of subjects (n=14,673) had the suspend feature activated 100% of the time, while 11% (n=2249) did not use that feature at all. The remaining 19% of subjects used the feature some unspecified portion of the time. On days when the threshold suspend feature was on, overall, there was an average of 0.82 suspend events per subject-day. In addition, glucose values were reported to be 50 mg/dL or less 0.64% of the time when the feature was on versus 2.1% of the time when the feature was off. The reduction in hypoglycemia was greatest at night. The authors concluded that the use of an automated insulin delivery device with threshold suspend appeared to be associated with fewer and shorter hypoglycemic episodes. However, the length and severity of hypoglycemic episodes was not fully described.

**Insulin-Only APD Systems**

**Randomized Controlled Trials**

In 2016, Ly et al. published the results of a small RCT which evaluated the experimental predecessor to the MiniMed 670G insulin-only system, including 21 children and adolescents with type 1 diabetes at diabetes camp. During the camp study, 21 subjects completed 50 overnight closed-loop (OCL) nights and 52 control nights with only sensor-augmented therapy. The median time spent in range (70 to 150 mg/dL) was significantly greater during OCL at 66.4% (n = 55) versus 50.6% (n = 52) during the control period (p = 0.004). In addition, the investigators reported that less time was spent in the hypoglycemic ranges <60 mg/dL and <70 mg/dL during OCL compared with the control period (p = 0.003 and p < 0.001, respectively), indicating that the hybrid closed loop system is effective in improving time spent in range as well as reducing nocturnal hypoglycemia during the overnight period in children and adolescents with type 1 diabetes in a diabetes camp setting.

**Nonrandomized Studies**

Prior to the FDA approval of the MiniMed 670G, in 2016, Ly et al. published a small case series evaluating the hybrid system in nine adults and 15 adolescents in supervised hotel-based studies over four to five days. The overall mean percentage of time in range (70–180 mg/dL, 3.9–10 mmol/L) during...
hybrid closed-loop was 71.8% in the adult cohort and 69.8% in the adolescent cohort. The overall percentage of time spent under 70 mg/dL (3.9 mmol/L) was 2.0% in the adult cohort and 2.5% in the adolescent cohort. Mean glucose values were 152 mg/dL (8.4 mmol/L) in the adult cohort and 153 mg/dL (8.5 mmol/L) in the adolescent cohort.

In 2016, Bergenstal et al. published the results of an investigational device exemption (IDE) study designed to assess the safety of the MiniMed 670G, including adolescents (n = 30, ages 14-21 years) and adults (n = 94, ages 22-75 years) who had type 1 diabetes mellitus for at least 2 years, HbA1c less than 10.0%, and prior insulin pump therapy for a minimum of 6 months. All subjects wore the 670G system for approximately 3.5 months. All subjects underwent a two week in-home run-in phase using the 670G in Manual mode (sensor-augmented pump) followed by a 3 month phase when the system was used in auto “hybrid” mode to automatically adjust basal insulin levels. During the auto phase, all subjects underwent a 6 day/5 night supervised hotel stay that included a 24-hour blood sampling period to compare glucose sensor measurements to lab-based venous blood glucose measurements. The purpose of the hotel phase was to stress the subjects with sustained daily exercise and unrestricted eating to monitor the device’s response to significant physiological variations. The authors reported that no episodes of severe hypoglycemia or ketoacidosis were noted during the study period. There were 20 device-related adverse events reported during the study period, including skin irritation or rash (n=2), hyperglycemia (n=6), and severe hyperglycemia (defined as greater than 300 mg/dL, n=12). All events were resolved at home. The closed-loop auto function was used for a median of 87.2% of the study period. The authors reported that their study demonstrated that hybrid closed-loop automated insulin delivery was associated with few serious or device-related adverse events in individuals with type 1 diabetes. Limitations, as reported by the authors, included a lack of a control group or randomization, relatively short study duration and an imbalance between the lengths of the three study periods. They concluded that longer-term randomized studies were needed to further evaluate the safety and efficacy of the 670G system.

In 2017, Garg et al. published additional results from the same study cohort used by Bergenstal et al., described above. In this publication, the authors reported that during the auto phase, the mean in-target glucose sensor reading in the adolescent group increased from 60.4% to 67.2% between the run-in to the auto phase (p<0.001). For the adult group, the mean in-target glucose sensor reading went from 68.8% to 73.8% (p<0.001). Similarly, time with glucose sensor readings of > 180 mg/dL decreased from 35.3% to 30.0% in the adolescent group (p<0.001) and 24.9% to 22.8% in the adult group (p<0.01). The mean time with sensor glucose readings < 70 mg/dL decreased from 4.3% to 2.8% in the adolescent group (p<0.0009) and 6.4% to 3.4% (p<0.001) in the adult group. Mean HbA1c concentrations decreased from 7.7% at baseline to 7.1% (p<0.001) at the end of the 3-month auto phase in the adolescent group and from 7.3% to 6.8% (p<0.001) in the adult group during the same time frame. The percent nighttime sensor glucose readings > 180 mg/dL decreased from 30.3% to 25.6% (p<0.001) in the adolescent group and 25.8% to 20.4% (p<0.001) in the adult group. Similarly, mean nighttime sensor glucose readings < 50 mg/dL decreased from 1.3% to 0.6% in the adolescent group (p<0.001) and 1.1 to 0.7% (p<0.001) in the adult group. Additional limitations not described above include restriction to relatively healthy and well-controlled patients and low baseline HbA1c, which limits the generalizability of the results. Regardless, the investigators concluded that the 670G, when operating in auto “hybrid” mode, was safe and effective.
mode provided significantly better blood glucose control over the use of the device while in manual sensor-augmented therapy mode.

**Bi-Hormonal APD Systems**

**Randomized Controlled Trials**

In 2015, Haidar et al. published results from a Canadian open-label randomized controlled crossover trial that compared dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy (plus self-monitoring of blood glucose) for glycemic control in patients aged 12 years or older with type 1 diabetes. Of the 40 patients recruited and randomized, only 30 patients (20 adults and 10 adolescents) completed the study and were included in the analysis. The mean proportion of time spent in the plasma glucose target range (4.0-10.0 mmol/L for 2-hours post-prandially and 4.0-8.0 mmol/L otherwise) over 24 hours was 62% (SD 18%), 63% (SD 18%), and 51% (SD 19%) with single-hormone artificial pancreas, dual-hormone artificial pancreas, and conventional insulin pump therapy, respectively. The mean difference in time spent in the target range between single-hormone artificial pancreas and conventional insulin pump therapy was 11% (p=0.002) and between dual-hormone artificial pancreas and conventional insulin pump therapy was 12% (p=0.0001), indicating that both the single- and dual-hormone systems were more effective than conventional CSII at maintaining glucose levels within a healthy target range. There was no difference in the proportion of time spent in the target range between the single-hormone and dual-hormone artificial pancreas systems. In addition, the percentage of patients in each group with at least one hypoglycemic event between single-hormone artificial pancreas and conventional insulin pump therapy was 17% and 83%, respectively (p<0.0001) and between dual-hormone artificial pancreas and conventional insulin pump therapy was 21% and 83%, respectively (p=0.0001), indicating that both the single- and dual-hormone systems were more effective than conventional CSII at reducing hypoglycemic events. This was true for both the total number of events as well as nocturnal and exercise-induced events. There was no difference in hypoglycemic events between the single-hormone and dual-hormone artificial pancreas systems. Limitations of this study include: small sample size, high drop-out rate, and the fact that the study was performed strictly in an inpatient setting and only for the duration of one day.

**CLINICAL PRACTICE GUIDELINES**

**American Diabetes Association (ADA)**

In 2019, the ADA “Standards of Medical Care in Diabetes” evidence-based guidelines made the following recommendations for insulin pumps:

- “Most adults, children and adolescents with type 1 diabetes should be treated with intensive insulin therapy with either multiple daily injections or an insulin pump.”
**MEDICAL POLICY**

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<th>Diabetes: Integrated Insulin Infusion and Glucose Monitoring Systems (All Lines of Business Except Medicare)</th>
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- “Insulin pump therapy may be considered as an option for all children and adolescents, especially in children under 7 years of age.”
- Automated insulin delivery systems may be considered in children more than 7 years of age and adults with type 1 diabetes to improve glycemic control.

ADA recommendations for continuous glucose monitoring include:

- “Sensor-augmented pump therapy may be considered for children, adolescents, and adults to improve glycemic control without an increase in hypoglycemia or severe hypoglycemia.”
- “Sensor-augmented pump therapy with automatic low-glucose suspend may be considered for adults with type 1 diabetes at high risk at hypoglycemia to prevent episodes of hypoglycemia and reduce their severity.”

The ADA stated that automated insulin delivery systems may lower the risk of exercise-related hypoglycemia and may confer psychosocial benefits.

**National Institute for Health and Care Excellence (NICE)**

In 2016, the National Institute for Health and Care Excellence (NICE) published an evidence-based guideline on use of the MiniMed Paradigm Veo system (the European equivalent of the MiniMed 530G). Recommendations were as follows:

- “The MiniMed Paradigm Veo system is recommended as an option for managing blood glucose levels in people with type 1 diabetes only if:
  - They have episodes of disabling hypoglycaemia (defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life); despite optimal management with continuous subcutaneous insulin infusion, and
  - The MiniMed Paradigm Veo system should be used under the supervision of a trained multidisciplinary team who are experienced in continuous subcutaneous insulin infusion and continuous glucose monitoring for managing type 1 diabetes only if the person or their carer:
    - Agrees to use the sensors for at least 70% of the time
    - Understands how to use it and is physically able to use the system, and
    - Agrees to use the system while having a structured education programme on diet and lifestyle, and counselling.
- People who start to use the MiniMed Paradigm Veo system should only continue to use it if they have a decrease in the number of hypoglycaemic episodes that is sustained. Appropriate targets for such improvements should be set.”

**American Diabetes Association (ADA)**
In 2018, the AACE/ACE published a joint clinical practice guideline on the integration of insulin pumps and continuous glucose monitoring in patients with diabetes mellitus. This guideline is primarily based in evidence.

The panel recommended that integration of CHM and CSII may be considered in patients already on CSII or appropriate for initiating CSII. Investigators noted that the ideal approach of integrating CSII and CGM is still under investigation.

The 2017, the ADA “Standards of Medical Care in Diabetes” evidence-based guidelines do not included artificial pancreas devices in their recommendations. However, they state the following:

- Threshold suspend devices may offer the opportunity to reduce hypoglycemia for those with a history of nocturnal hypoglycemia.
- The first hybrid closed-loop system approved by the FDA may be considered as an option in those already on an insulin pump. The association believes that the safety of hybrid closed-loop systems has been supported in the literature.

American Association of Clinical Endocrinologists / American College of Endocrinology (AACE/ACE)

In 2015, the AACE/ACE published a joint clinical practice guideline for developing a diabetes mellitus comprehensive care plan. This guideline is primarily based in evidence.

The panel recommended that sensor-augmented CSII, including those with a threshold-suspend function, should be considered for patients who are at risk of hypoglycemia. This was a strong recommendation, based on strong evidence.

- In 2018, the AACE/ACE published a joint clinical practice guideline on the integration of insulin pumps and continuous glucose monitoring in patients with diabetes mellitus. This guideline is primarily based in evidence.

The panel recommended that integration of CHM and CSII may be considered in patients already on CSII or appropriate for initiating CSII. Investigators noted that the ideal approach of integrating CSII and CGM is still under investigation.

**POLICY SUMMARY**

Insulin pumps that have the ability to read and display data from continuous glucose monitors (CGM) are commonly called integrated continuous subcutaneous insulin infusion (CSII) – CGM system. Integrated systems that have no automation are referred to as sensor-augmented systems, and have been shown to improve various measures of glycemic control. The evidence regarding the efficacy of sensor-augmented systems consists of several randomized controlled trials with moderately-sized study cohorts, as well as large case series. These studies indicated that patients using sensor-augmented
systems have significantly lower HbA1c levels and fewer hypoglycemic episodes than patients using CSII and self-monitoring of blood glucose (SMBG), and patients using multiple daily insulin injections and SMBG.

Integrated systems that have various levels of automation are referred to as the FDA as artificial pancreas device systems (APDS). APDSs that have a threshold suspend (or low-glucose suspend) mode, including the MiniMed 530G and 630G systems, have been studied in several medium- to large-sized randomized controlled trials and one very large retrospective analysis (over 20,000 patients). Studies evaluating the first insulin-only APDS, referred to as the hybrid MiniMed670G system, consists of one small RCT and several small but compelling trials. There is consistent evidence that both threshold suspend and insulin-only APDSs reduce the number and duration of total and nocturnal hypoglycemic events in children, adolescents and adults compared to sensor-augmented systems.

Lastly, studies on experimental bi-hormonal APDS, referred to as “true” closed-loop, fully automated APDS are emerging. There are no bi-hormonal APDSs that have been approved by the FDA at this time, and the evidence currently consists of small in-patient “proof-of-concept” studies.

### INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

### REGULATORY STATUS

**Mental Health Parity Statement**

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

### MEDICAL POLICY CROSS REFERENCES

- Diabetes: Integrated Insulin Infusion and Glucose Monitoring Systems (Medicare Only), DME397
MEDICAL POLICY

Diabetes: Integrated Insulin Infusion and Glucose Monitoring Systems
(All Lines of Business Except Medicare)

- Diabetes: Insulin Infusion Pumps – External and Implanted (All Lines of Business Except Medicare), DME208
- Diabetes: Insulin Infusion Pumps – External and Implanted (Medicare Only), DME414
- Diabetes: Blood Glucose Monitor and Supplies, DME206
- Diabetes: Continuous Glucose Monitors (All Lines of Business Except Medicare), DME207
- Diabetes: Continuous Glucose Monitors (Medicare Only), DME392

REFERENCES


