Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

RELATED PROTOCOLS

Allogeneic Pancreas Transplant

Continuous or Intermittent Monitoring of Glucose in the Interstitial Fluid

Islet Transplantation

<table>
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<th>Populations</th>
<th>Interventions</th>
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<td>Relevant outcomes include:</td>
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<td>• Artificial pancreas device system with a low-glucose suspend feature</td>
<td>• Nonintegrated continuous glucose monitoring plus insulin pump</td>
<td>• Symptoms</td>
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<tr>
<td></td>
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<td>• Self-monitoring blood glucose and multiple dose insulin injection therapy</td>
<td>• Change in disease status</td>
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<td></td>
<td>• Treatment-related morbidity</td>
</tr>
</tbody>
</table>

DESCRIPTION

Automated insulin delivery systems, also known as artificial pancreas device systems, link a glucose monitor to an insulin infusion pump that automatically takes action (e.g., suspends or adjusts insulin infusion) based on the
Protocol: Artificial Pancreas Device Systems

Last Review Date: 01/22

Glucose monitor reading. These devices are proposed to improve glycemic control in patients with insulin-dependent diabetes, in particular, reduction of nocturnal hypoglycemia.

SUMMARY OF EVIDENCE

For individuals who have type 1 diabetes who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence includes 2 randomized controlled trials (RCTs) conducted in home settings. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Primary eligibility criteria of the key RCT, the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, were ages 16-to-70 years old, type 1 diabetes, glycated hemoglobin levels between 5.8% and 10.0%, and at least 2 nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. Both trials required at least 6 months of insulin pump use. Both RCTs reported significantly less hypoglycemia in the treatment group than in the control group. In both trials, primary outcomes were favorable for the group using an artificial pancreas system; however, findings from 1 trial were limited by non-standard reporting of hypoglycemic episodes, and findings from the other trial were no longer statistically significant when 2 outliers (children) were excluded from analysis. The RCT limited to adults showed an improvement in the primary outcome (area under the curve for nocturnal hypoglycemic events). The area under the curve is not used for assessment in clinical practice but the current technology does allow user and provider review of similar trend data with continuous glucose monitoring. Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential diabetic ketoacidosis in subjects using the threshold suspend feature. This finding may be related to whether or not actions are taken by the user to assess glycemic status, etiology of the low glucose (activity, diet or medication), and to resume insulin infusion. Both retrospective and prospective observational studies have reported reductions in rates and severity of hypoglycemic episodes in automated insulin delivery system users. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the type 1 diabetes population is likely to be clinically significant. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have type 1 diabetes who receive an artificial pancreas device system with a hybrid closed-loop insulin delivery system, the evidence includes multicenter pivotal trials using devices cleared by the U.S. Food and Drug Administration, supplemental data and analysis for expanded indications, and more recent studies focused on children and adolescents. Three crossover RCTs using a similar first-generation device approved outside the United States have been reported. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Of the 3 crossover RCTs assessing a related device conducted outside the United States, 2 found significantly better outcomes (i.e., time spent in nocturnal hypoglycemia and time spent in preferred glycemic range) with the device than with standard care and the other had mixed findings (significant difference in time spent in nocturnal hypoglycemia and no significant difference in time spent in preferred glycemic range). For the U.S. regulatory registration pivotal trial, the primary outcomes were safety and not efficacy. Additional evidence from device performance studies and clinical studies all demonstrate reductions in time spent in various levels of hypoglycemia, improved time in range (70-180 mg/dl), rare diabetic ketoacidosis, and few device-related adverse events. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the type 1 diabetes population is likely to be clinically significant. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

POLICY

Use of an FDA-approved automated insulin delivery system (artificial pancreas device system) designated as hy-
brid closed-loop insulin delivery system (with low glucose suspend and suspend before low features) may be considered **medically necessary** in patients with type 1 diabetes who meet all of the following criteria:

- Over 6 years and older AND
  - Glycated hemoglobin level between 5.8% and 10.0%
  - At least two documented nocturnal hypoglycemic events in a two-week period.

OR

- Age 2 to 6 years AND
  - Glycated hemoglobin level <10.0%
  - At least two documented nocturnal hypoglycemic events in a two-week period
  - Minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units

Use of an automated insulin delivery system (artificial pancreas device system) is **investigational** for individuals who do not meet the above criteria.

Use of an automated insulin delivery system (artificial pancreas device system) not approved by the Food and Drug Administration is **investigational**.

**BACKGROUND**

**DIABETES AND GLYCEMIC CONTROL**

Tight glucose control in patients with diabetes has been associated with improved health outcomes. The American Diabetes Association has recommended a glycated hemoglobin level below 7% for most patients. However, hypoglycemia, may place a limit on the ability to achieve tighter glycemic control. Hypoglycemic events in adults range from mild to severe based on a number of factors including the glucose nadir, the presence of symptoms, and whether the episode can be self-treated or requires help for recovery. Children and adolescents represent a population of type 1 diabetics who have challenges in controlling hyperglycemia and avoiding hypoglycemia. Hypoglycemia is the most common acute complication of type 1 diabetes.

Table 1 is a summary of selected clinical outcomes in type 1 diabetes clinical management and research.

**Table 1. Outcome Measures for Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition</th>
<th>Guideline type</th>
<th>Organization</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td>Stakeholder survey, expert opinion with evidence review</td>
<td>Type 1 Diabetes Outcome Program¹</td>
<td>2017</td>
</tr>
<tr>
<td>Level 1</td>
<td>Glucose &lt;70 mg/dl but ≥54 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 2</td>
<td>Glucose &lt;54 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 3</td>
<td>Event characterized by altered mental/physical status requiring assistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Same as Type 1 Diabetes Outcome Program⁷</td>
<td>Professional Practice Committee with systematic literature review</td>
<td>ADA²</td>
<td>2019</td>
</tr>
</tbody>
</table>
**Measure** | **Definition** | **Guideline type** | **Organization** | **Date**
---|---|---|---|---
**Hypoglycemia** | Glucose <70 mg/dl | Clinical Practice Consensus | ISPAD<sup>3</sup> | 2018
| Clinical alert for evaluation and/or treatment | Glucose <54 mg/dl | | | 
| Clinically important or severe | Severe cognitive impairment requiring external assistance by another person to take corrective action | | | 
**Hyyperglycemia** | Glucose >180 mg/dL and ≤250 mg/dL | Type 1 Diabetes Outcome Program<sup>a</sup> | 2017
| Level 2 | Glucose >250 mg/dL | | | 
| Time in Range<sup>b</sup> | Percentage of glucose readings in the range of 70–180 mg/dL per unit of time | | | 
| Diabetic ketoacidosis (DKA) | Elevated serum or urine ketones >ULN Serum bicarbonate <15 mEq/L Blood pH <7.3 | Type 1 Diabetes Outcome Program<sup>a</sup> | 2017

ADA: American Diabetes Association, ISPAD: International Society for Pediatric and Adolescent Diabetes; ULN: upper limit of normal.

<sup>a</sup>Steering Committee: representatives from American Association of Clinical Endocrinologists (AACE), American Association Diabetes Educators, the American Diabetes Association (ADA), the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, type 1 diabetes Exchange

<sup>b</sup>Time in range: has also been adopted by researchers evaluating the precision and effectiveness of emerging glucose monitoring and automated insulin delivery technologies.

**Treatment**

Type 1 diabetes is caused by the destruction of the pancreatic beta cells which produce insulin, and the necessary mainstay of treatment is insulin injections. Multiple studies have shown that intensive insulin treatment, aimed at tightly controlling blood glucose, reduces the risk of long-term complications of diabetes, such as retinopathy and renal disease. Optimal glycemic control, as assessed by glycated hemoglobin, and avoidance of hyper- and hypoglycemic excursions have been shown to prevent diabetes-related complications. Currently, insulin treatment strategies include either multiple daily insulin injections or continuous subcutaneous insulin infusion with an insulin pump.

The use of the continuous glucose monitoring component of diabetes self-management is specifically addressed in the Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid Protocol.

**REGULATORY STATUS**

The U.S. Food and Drug Administration (FDA) describes the basic design of an artificial pancreas device system as a continuous glucose monitoring linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on specified thresholds of measured interstitial glucose.<sup>5</sup>

The artificial pancreas device system components are designed to communicate with each other to automate the process of maintaining blood glucose concentrations at or near a specified range or target and to minimize the incidence and severity of hypoglycemic and hyperglycemic events. An artificial pancreas device system control algorithm is embedded in software in an external processor or controller that receives information from the continuous glucose monitoring and performs a series of mathematical calculations. Based on these calculations, the controller sends dosing instructions to the infusion pump.

Different artificial pancreas device system types are currently available for clinical use. Sensor augmented pump therapy with low glucose suspend (suspend on low) may reduce the likelihood or severity of a hypoglycemic
event by suspending insulin delivery temporarily when the sensor value reaches (reactive) a predetermined lower threshold of measured interstitial glucose. Low glucose suspension automatically suspends basal insulin delivery for up to 2 hours in response to sensor-detected hypoglycemia.

A sensor augmented pump therapy with predictive low glucose management (suspend before low) suspends basal insulin infusion with the prediction of hypoglycemia. Basal insulin infusion is suspended when sensor glucose is at or within 70 mg/dL above the patient-set low limit and is predicted to be 20 mg/dL above this low limit in 30 minutes. In the absence of a patient response, the insulin infusion resumes after a maximum suspend period of 2 hours. In certain circumstances, auto-resumption parameters may be used.

When a sensor value is above or predicted to remain above the threshold, the infusion pump will not take any action based on continuous glucose monitoring readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump, and give premeal bolus insulin to control their glucose levels.

A control-to-range system reduces the likelihood or severity of a hypoglycemic or hyperglycemic event by adjusting insulin dosing only if a person’s glucose levels reach or approach predetermined higher and lower thresholds. When a patient’s glucose concentration is within the specified range, the infusion pump will not take any action based upon continuous glucose monitoring readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump, and give premeal bolus insulin to control their glucose levels.

A control-to-target system sets target glucose levels and tries to maintain these levels at all times. This system is fully automated and requires no interaction from the user (except for calibration of the continuous glucose monitoring). There are 2 subtypes of control-to-target systems: insulin-only and bihormonal (e.g., glucagon). There are no systems administering glucagon marketed in the United States.

An artificial pancreas device system may also be referred to as a “closed-loop” system. A closed-loop system has automated insulin delivery and continuous glucose sensing and insulin delivery without patient intervention. The systems utilize a control algorithm that autonomously and continually increases and decreases the subcutaneous insulin delivery based on real-time sensor glucose levels. There are no completely closed-loop insulin delivery systems marketed in the United States.

A hybrid closed-loop system also uses automated insulin delivery with continuous basal insulin delivery adjustments. However, at mealtimes, the patient enters the number of carbohydrates they are eating in order for the insulin pump to determine the bolus meal dose of insulin. A hybrid system option with the patient administration of a premeal or partial premeal insulin bolus can be used in either control-to-range or control-to-target systems.

These systems are regulated by the FDA as class III device systems.

Table 2 summarizes the FDA-approved automated insulin delivery systems.

<table>
<thead>
<tr>
<th>Device</th>
<th>Age Indication</th>
<th>Manufacturer</th>
<th>Date Approved</th>
<th>PMA No./Device Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>MiniMed 530G System&lt;sup&gt;a&lt;/sup&gt; (open-loop, LGS)</td>
<td>≥16 y</td>
<td>Medtronic</td>
<td>Jul 2013</td>
<td>P120010/OZO</td>
</tr>
<tr>
<td>MiniMed 630G System with SmartGuard&lt;sup&gt;b&lt;/sup&gt; (open-loop, LGS)</td>
<td>≥16 y, ≥14 y</td>
<td>Medtronic</td>
<td>Aug 2016, Jun 2017</td>
<td>P150001/OZO, P150001/S008</td>
</tr>
<tr>
<td>MiniMed 670G System&lt;sup&gt;c&lt;/sup&gt; (HCL, LGS or PLGM)</td>
<td>≥14 y, ≥7-13 y</td>
<td>Medtronic</td>
<td>Sep 2016, Jul 2018</td>
<td>P160017/OZR, P160017/S031</td>
</tr>
<tr>
<td>MiniMed 770G System&lt;sup&gt;d&lt;/sup&gt; (HCL)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>≥2 y</td>
<td>Medtronic</td>
<td>Aug 2020</td>
<td>P160017/S076</td>
</tr>
<tr>
<td>t:slim X2 Insulin Pump with Basal-IQ Technology (LGS)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>≥6 y</td>
<td>Tandem</td>
<td>Jun 2018</td>
<td>P180008/OZO, PQF</td>
</tr>
<tr>
<td>t:slim X2 Insulin Pump with Control-IQ Technology (HCL)</td>
<td>≥6 y</td>
<td>Tandem</td>
<td>Dec 2019</td>
<td>DEN180058/QFG</td>
</tr>
</tbody>
</table>
The MiniMed 670G System includes a threshold suspend or low glucose suspend feature. The threshold suspend tool temporarily suspends insulin delivery when the sensor glucose level is at or below a preset threshold within the 60- to 90-mg/dL range. When the glucose value reaches this threshold, an alarm sounds. If patients respond to the alarm, they can choose to continue or cancel the insulin suspend feature. If patients fail to respond, the pump automatically suspends action for 2 hours, and then insulin therapy resumes.

The MiniMed 530G System consists of the following devices: MiniMed 530G Insulin Pump, the Guardian Sensor (3), One-Press Serter, Guardian® Link Transmitter System, CareLink® Professional Therapy Management Software for Diabetes, and CareLink® Personal Therapy Management Software for Diabetes (at time of approval).

The MiniMed 630G System with SmartGuard™ consists of the following devices: MiniMed 630G Insulin Pump, Enlite® Sensor, One-Press Serter, Guardian® Link Transmitter System, CareLink® USB, Bayer’s CONTOUR® NEXT LINK 2.4 Wireless Meter, and Bayer’s CONTOUR® NEXT Test Strips (at time of approval).

The MiniMed 670G System consists of the following devices: MiniMed 670G Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), One-Press Serter, and the Contour NEXT Link 2.4 Glucose Meter (at time of approval). MiniMed 770G System consists of the following devices: MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips.

The MiniMed 530G System consists of the following devices that can be used in combination or individually: MiniMed 530G Insulin Pump, Enlite™ Sensor, Enlite™ Serter, the MiniLink Real-Time System, the Bayer Contour NextLink glucose meter, CareLink® Professional Therapy Management Software for Diabetes, and CareLink® Personal Therapy Management Software for Diabetes (at time of approval).

The MiniMed 770G System is an iteration of the MiniMed 670G System. In July 2020, the device was approved for use in children ages 2 to 6 years. In addition to the clinical studies that established the safety and effectiveness of the MiniMed 670G System in users ages 7 years and older, the sponsor performed clinical studies of the 670G System in pediatric subjects ages 2 to 6 years. FDA concluded that these studies establish a reasonable assurance of the safety and effectiveness of the MiniMed 770G System because the underlying therapy in the 670G system, and the associated Guardian Sensor (3), are identical to that of the 770G System.

On June 21, 2018, the FDA approved the t:slim X2 Insulin Pump with Basal-IQ Technology (PMA P180008) for individuals who are 6 years of age and older. The System consists of the t:slim X2 Insulin Pump paired with the Dexcom G5 Mobile Continuous Glucose Monitoring, as well as the Basal-IQ Technology. The t:slim X2 Insulin Pump is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of dia-
betes mellitus in persons requiring insulin. The t:slim X2 Insulin Pump can be used solely for continuous insulin delivery and as part of the System as the receiver for a therapeutic continuous glucose monitoring. The t:slim X2 Insulin Pump running the Basal-IQ Technology can be used to suspend insulin delivery based on continuous glucose monitoring sensor readings.

In December 2019, FDA approved the t:slim X2 Insulin Pump with Control-IQ Technology through the De Novo process. The device uses the same pump hardware as the insulin pump component of the systems approved in t:slim X2 Insulin Pump with Basal-IQ Technology (P180008) and P140015. A custom disposable cartridge is motor-driven to deliver patient programmed basal rates and boluses through an infusion set into subcutaneous tissue.

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REFERENCES

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