Artificial Pancreas Device Systems

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

OBJECTIVE

The objective of this evidence review is to determine whether artificial pancreas device systems improve the net health outcome in patients with type 1 diabetes compared with standard glucose monitoring, either continuous glucose monitoring (CGM) or self-monitoring of blood glucose (SMBG), plus an insulin pump or multiple insulin injection therapy.

POLICY STATEMENT

Use of a U.S. Food and Drug Administration–approved automated insulin delivery system (artificial pancreas device system) with a low-glucose suspend feature may be considered medically necessary in patients with type 1 diabetes who meet all of the following criteria:

- Age 14 and older
- Glycated hemoglobin level between 5.8% and 10.0%
- Used insulin pump therapy for more than 6 months
- At least 2 documented nocturnal hypoglycemic events in a 2-week period.

Use of a Food and Drug Administration–approved automated insulin delivery system (artificial pancreas device system) designated as hybrid 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:

- Age 7 and older
- Glycated hemoglobin level between 5.8% and 10.0%
- Used insulin pump therapy for more than 6 months
- At least 2 documented nocturnal hypoglycemic events in a 2-week period.

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.

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

The Food and Drug Administration (FDA) describes the basic design of an artificial pancreas device system (APDS) as a CGM linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on specified thresholds of measured interstitial glucose. 4

The APDS 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 APDS control algorithm is embedded in software in an external processor or 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.

Different APDS types are currently available for clinical use. Sensor augmented pump therapy (SAPT) with low glucose suspend (LGS) (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 (LGS) automatically suspends basal insulin delivery for up to two hours in response to sensor-detected hypoglycemia.

A sensor augmented pump therapy with predictive low glucose management (PLGM) (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 two 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 CGM 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 CGM 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 CGM). There are two subtypes of control-to-target systems: insulin-only and bihormonal (eg, glucagon). There are no systems administering glucagon marketed in the United States.

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An APDS 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 mealtime, 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 1 summarizes the FDA-approved automated insulin delivery systems.

Table 1. FDA-Approved Automated Insulin Delivery Systems (Artificial Pancreas Device 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</td>
<td>Medtronic</td>
<td>Aug 2016</td>
<td>P150001/OZO</td>
</tr>
<tr>
<td></td>
<td>≥14 y</td>
<td></td>
<td>Jun 2017</td>
<td>P150001/S008</td>
</tr>
<tr>
<td>MiniMed 670G System&lt;sup&gt;c&lt;/sup&gt; (hybrid closed-loop, LGS or PLGM)</td>
<td>≥14 y</td>
<td>Medtronic</td>
<td>Sep 2016</td>
<td>P160017/OZP</td>
</tr>
<tr>
<td></td>
<td>≥7-13 y</td>
<td></td>
<td>Jul 2018</td>
<td>P160017/S031</td>
</tr>
</tbody>
</table>


<sup>a</sup> 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).

<sup>b</sup> 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).

<sup>c</sup> 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).

The MiniMed 530G System includes a threshold suspend or LGS feature.<sup>5</sup> 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 two hours, and then insulin therapy resumes.

The MiniMed 630G System with SmartGuard™, which is similar to the 530G, includes updates to the system components including waterproofing.<sup>6</sup> The threshold suspend feature 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. The MiniMed 630G System with SmartGuard™ is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be necessary.
required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on the values provided by the MiniMed 630G system. The device is 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 SmartGuard™ Suspend on Low alarm to take measures to prevent or treat hypoglycemia themselves.

The MiniMed 670G System is a hybrid closed-loop insulin delivery system consisting of an insulin pump, a glucose meter, and a transmitter, linked by a proprietary algorithm and the SmartGuard Hybrid Closed Loop. The system includes an LGS feature that suspends insulin delivery; this feature either suspends delivery on low-glucose levels or suspends delivery before low-glucose levels, and has an optional alarm (manual mode). Additionally, the system allows semiautomatic basal insulin-level adjustment (decrease or increase) to preset targets (automatic mode). As a hybrid system; basal insulin levels are automatically adjusted, but the patient needs to administer premeal insulin boluses. The CGM component of the MiniMed 670G System is not intended to be used directly for making manual insulin therapy adjustments; rather it is to provide an indication of when a glucose measurement should be taken.

The most recent supplemental approval for the MiniMed 670G System in July 2018 followed the granting a designation of breakthrough device status.

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 CGM (Continuous Glucose Monitor), 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 diabetes 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 CGM. The t:slim X2 Insulin Pump running the Basal-IQ Technology can be used to suspend insulin delivery based on CGM sensor readings. Introduction into clinical care is planned for summer 2019.

**RATIONALE**

**Summary of Evidence**

For individuals who have type 1 diabetes (T1D) who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence includes two 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, T1D, glycated hemoglobin levels between 5.8% and 10.0%, and at least 2 nocturnal hypoglycemic events (≤85 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. Both trials required at least six 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 one trial were limited by nonstandard reporting of hypoglycemic episodes, and findings from the other trial were no longer statistically significant when two 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 T1D population is likely to be clinically significant. Limitations of the published evidence preclude determining the effects of the technology on overall glycemic control as assessed by HbA1c and other parameters and thus, net health outcomes. Evidence reported through clinical input supports that the outcome of hypoglycemia prevention provides a clinically meaningful improvement in net health outcome, and this use is consistent with generally accepted medical practice. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have T1D 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 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 three crossover RCTs assessing a related device conducted outside the United States, two found significantly better outcomes (ie, 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). 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 T1D population is likely to be clinically significant. Limitations of the published evidence preclude determining the effects of the technology on overall glycemic control as assessed by HbA1c and other parameters and thus, net health outcomes. Evidence reported through clinical input supports that the outcome of hypoglycemia prevention provides a clinically meaningful improvement in net health outcome, and this use is consistent with generally accepted medical practice. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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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 (70-180mg/dl), rare diabetic ketoacidosis and few device-related adverse events. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the T1D population is likely to be clinically significant. The variations in the definition of primary and secondary outcomes in the study design and conduct of the published evidence are limitations that preclude determining the effects of the technology on net health outcomes. Evidence reported through clinical input supports that the use of hybrid closed loop APDS systems provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. Reduction in the experience of hypoglycemia and inappropriate awareness of hypoglycemia and glycemic excursions were identified as important acute clinical outcomes in children, adolescents, and adults and are related to the future risk for end-organ complications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Diabetes Association

The American Diabetes Association has released multiple publications on controlling type 1 diabetes (see Table 2).

Table 2. Recommendations on Diabetes

<table>
<thead>
<tr>
<th>Date</th>
<th>Title</th>
<th>Publication Type</th>
<th>Recommendation</th>
<th>LOE</th>
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<tbody>
<tr>
<td>2018</td>
<td>Type 1 Diabetes in Children and Adolescents</td>
<td>Position statement&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Automated insulin delivery systems appear to improve glycemic control and reduce hypoglycemia in children and should be considered in pediatric patients with type 1 diabetes</td>
<td>B</td>
</tr>
<tr>
<td>2019</td>
<td>Standards of Medical Care in Diabetes</td>
<td>Guideline standard&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Automated insulin delivery systems improve glycemic control and reduce hypoglycemia in adolescents and should be considered in adolescents with type 1 diabetes</td>
<td>B</td>
</tr>
<tr>
<td>2017</td>
<td>Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes</td>
<td>Consensus report&lt;sup&gt;1&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Developed definitions for hypoglycemia, hyperglycemia, time in range, and diabetic ketoacidosis in type 1 diabetes</td>
<td>N/A</td>
</tr>
</tbody>
</table>

LOE: Level of Evidence.

<sup>a</sup> Jointly published with American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange.

American Association of Clinical Endocrinologists et al

The American Association of Clinical Endocrinologists and American College of Endocrinology (2018) published a joint position statement on the integration of insulin pumps and continuous glucose monitoring in patients with diabetes.<sup>24</sup> The statement emphasized the use of continuous glucose monitoring and insulin pump therapy for type 1 diabetes patients who are not in glycemic target ranges despite intensive attempts at self-blood glucose monitoring and multiple insulin injection therapy.

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U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


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**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>March 2015</td>
<td>New policy</td>
<td>Policy created with information on this topic previously addressed in Policy No. 1.01.20 and a literature review through December 20, 2014. FDA-approved artificial pancreas device system with low glucose suspend feature may be considered medically necessary for patients with type 1 diabetes who meet criteria; otherwise artificial pancreas device systems are considered not medically necessary.</td>
</tr>
<tr>
<td>June 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 1, 2015; references 6, 11, and 12 added. Policy statements unchanged.</td>
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<tr>
<td>March 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 15, 2017; references 1, 9, and 14 added. Per FEP PMPC, policy statement added that use of hybrid closed loop insulin delivery system as an artificial pancreas device system (including the Food and Drug Administration–approved device for age 14 and older) is considered medically necessary.</td>
</tr>
<tr>
<td>May 2019</td>
<td>Replace policy</td>
<td>The statement for FDA-approved automated insulin delivery system (artificial pancreas device system) designated as hybrid closed loop insulin delivery system in patients with type 1 diabetes who meet specified criteria was corrected from &quot;not medically necessary&quot; to &quot;medically necessary&quot;.</td>
</tr>
<tr>
<td>June 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 25, 2019, references 2, 17-21, and 23 added. Policy statements changed: The age criterion changed in the first medically necessary statement; and investigational statement added on use of an automated insulin delivery system (artificial pancreas device system) for individuals who have not met specified criteria.</td>
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