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Medical Policy

Subject:	**Ingestion Event Monitors**		
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Description/Scope

This document addresses ingestion event monitors for medication monitoring and adherence (ID-CAP™ System [etectRx™, Gainesville, FL], Discover® [Proteus Digital Health, Redwood City, CA]). Ingestion event monitors include a wireless sensor that is swallowed, a sensor worn outside of the body, a mobile device application for the recipient as well as an application utilized by medical professionals. This document does not address Abilify MyCite® (Otsuka America Pharmaceutical, Inc., Rockville, MD), which is specifically designed to be administered solely for monitoring and adherence of Abilify, an oral antipsychotic drug.

Position Statement

Investigational and Not Medically Necessary:

Ingestion event monitors are considered investigational and not medically necessary for medication monitoring and adherence and for all other indications.

Rationale

The use of ingestion event monitors has been investigated for medication monitoring to help ensure adherence to both standard of care and clinical trial treatment protocols. The available literature addresses two devices, the ID-CAP system, and the Discover system.

In 2013, Eisenberger and colleagues reported the results of a pilot study including 20 subjects to evaluate detection accuracy, usability, and safety of ingestible event monitors (IEMs) combined with enteric-coated mycophenolate sodium (ECMPS) over a mean of 9.2 weeks of follow-up. The subjects were in stable condition at least 6 months post-renal transplant and taking a stable dose of immunosuppressive therapy.

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The primary endpoints were detection accuracy when compared to direct observed ingestions (DOIs), overall medication adherence, and adherence to dosing schedule. Positive detection accuracy (PDA) was 100% (95% confidence interval [CI], 89.7-100%) for the 34 DOIs. There was a total of 4136 prescribed doses that occurred without direct observation, 2824 (68%) were successfully documented by the IEM. The doses that were not captured (n=1312) were likely due to subjects removing the adhesive personal monitor (APM). When the APM was worn, abnormal impedance was found in 16 of 1181 (1.4%) days of data collection; this is likely due to subjects wearing the APM longer than the recommended time period of 7 days. Overall medication adherence was 99.4% (95% CI, 99.0-99.6%); 17 of the missed doses were due to missed IEM detection as subjects reported compliance with dose adherence. Adherence to a dose scheduling was 84.5% (95% CI, 83.1-85.8%); the mean deviation from the time adherence window was 42 + 50 minutes. No serious adverse or rejection events were reported. Skin reactions to the APM occurred in 7 subjects with 2 of the subjects discontinuing use of the sensors due to rash. The study was small, limited in duration, and did not involve a control group. Long-term adherence outcomes, including health outcomes were also not evaluated by the study.

DiCarlo and colleagues (2016) published the results of a feasibility study consisting of 37 individuals with hypertension. Valsartan was combined with an IEM (Proteus Digital Health) to evaluate overall medication adherence and adherence to a dosing schedule. There were 510 witnessed doses and IEM captured 98% of the doses (PDA; 95% CI, 96.4-99.1%; p<0.05). The mean overall adherence was 90%, and the mean adherence to a dosing schedule was 83% with tapering noted in weeks 5 and 6. No serious adverse events were reported, but skin irritation events from the adhesive monitor were noted in 14 individuals (40%). No adverse events were reported related to the ingested sensor. The study was small, limited in duration, and did not involve a control group. Long-term adherence outcomes, including health outcomes were also not evaluated by the study.

A pilot study exploring the use, performance, and reliability of the ID-Cap System was published in 2016 by Flores and colleagues. This was an open-label, single-arm, 4-week study that enrolled 20 healthy subjects that ingested a total of 20 ID-Capsules. Endpoints included detection of the ingested capsule, utilization of the system, adverse events, and safety assessments regarding excretion of the sensor. The initial dose was directly observed with the subsequent 19 doses ingested independently. Each subject received a follow-up x-ray to assess if there was retention of the sensor. A total of 404 ID-Capsules were dispensed and the PDA was 100% for the directly observed first dose. The remaining 384 doses that were self-administered resulted in 371 data captures, for a total of 97.75% overall adherence (391/400, 4 individuals took an additional dose due to user error). The ID-Cap Readers uploaded data for 385 of the 391 (98.47%) events in real-time, the

data for the remaining 6 were successfully downloaded at the research center. The data included the time the sensor was detected in the stomach as well as the unique identification that was assigned to the sensor. There were no adverse events reported, and there was no evidence of sensors retained on follow-up imaging.

In 2017, Frias and colleagues reported the results of a clinical trial that studied the efficacy of Proteus Discover in subjects with uncontrolled hypertension and type 2 diabetes mellitus (T2DM). This trial was a 3-arm (IEM for 4 weeks, IEM for 12 weeks, or standard of care [SoC]), 12-week, cluster-randomized study that enrolled 109 subjects. Inclusion criteria included uncontrolled hypertension, defined as systolic BP (SBP) >140 mm Hg, T2DM with glycated hemoglobin A_{1c} (HbA_{1c}) >7%, despite use of greater than 2 antihypertensive medications and metformin or a sulfonylurea. The primary outcome of this study was the change in SBP from baseline to study completion at week 4. The results showed the subjects taking the medications with IEM had a mean decrease in SBP from baseline of 21.8 mm Hg (standard error [SE] 1.5 mm Hg) compared to SoC group that lowered their average SBP by 12.7 mm Hg (SE 2.8 mm Hg) (combined DMO–usual care: mean –9.1, SE 2.9, 95% CI –14.8 to –3.3 mm Hg; intracluster correlation coefficient [ICC]=0; adjusted difference: mean –10.0, SE 3.1, 95% CI –16.1 to –3.9 mm Hg; effect size=0.69). Secondary outcomes measured SBP to week 12 as well as HbA_{1c}, evaluated changes in diastolic BP and fasting glucose levels. There was a higher success rate of 81% (65/80) in achieving a BP goal within the IEM group versus 33.3% (9/27) within the SoC group (mean difference = 47.9% [SE 15.0%; 95% CI, 18.5-77.3%]). There was no significant difference in HbA_{1c} reduction at week 12 in the treatment group compared with SoC group. The mean ingestion adherence was 86% to week 4 and 84% through week 12. There was a total of 14 device-related adverse events in 11 subjects, with the most common event being mild skin reaction to the APM. The authors suggest that the improved outcomes were, in part, related to the IEM, the associated improved medication adherence and improved self-care. It was also noted that the providers assigned to the IEM groups made approximately three times more medical decisions per subject versus the SoC group, which included counseling and education. It is difficult to distinguish the success of the IEM directly if the providers were more involved in the care of their subjects versus the SoC group. A study with standardized provider care would help to discern if IEM alone can help with adherence and positive outcomes in subjects with uncontrolled hypertension and T2DM. Longer term studies are needed.

Browne and colleagues published the results of a randomized control trial (RCT) in 2019 comparing DOI with IEMs in subjects with active tuberculosis (TB). This study was separated into 2 stages; the first stage evaluated the accuracy of IEMs, and the second stage compared IEMs with DOI in adherence to TB continuation phase of treatment. Stage 1 consisted of 77 individuals and data was collected over 2 weeks; 16 individuals were excluded after stage 1, thereby 61 individuals continued to stage 2. In stage 2 the subjects

were randomized to IEM (n=41) or DOI (n=20) and continued until the end of treatment but not exceeding 12 months. The PDA estimate for stage 1 was 99.33% (680/685 person-days; 95% CI, 98.1-100.0%). There were 8 days documented for absent IEM data due to incorrect use. Stage 2 varied in duration depending on the arm that subjects were assigned to; the median duration was 99 days with no statistical difference between the arms (median 93 days compared to 101 days; p=0.85). The IEM group had 92.9% (3738/4022) of doses confirmed compared to 63.1% (1202/1904) of the DOI arm (p<0.001). The IEM group missed 284 (7.1%) doses, of those, 106 were held. If weekends, holidays, and held doses are removed from the DOI missed group statistics, the percent of confirmed doses in DOI is adjusted to 92.7% (95% CI, 86.7-96.9%), and the adjusted confirmed doses for IEM is 95.6% (95% CI, 93.6-97.2%). Therefore, the between group difference is only 2.8% (95% CI, -1.8-9.1%), showing that IEM was not significantly different from DOI. Adverse events were reported from 9.8% of subjects, with the majority being mild skin reactions to the patch associated with IEM. Additional well designed studies, with long term evaluation, are needed demonstrate improved health outcomes as a result of IEM. Study limitations include a small sample size and a lack of clinically relevant outcomes to elucidate the impact of IEM on the clinical course of TB.

Conceptually, ingestion event sensors offer the potential to improve medication adherence, and thus health outcomes. Currently, most published studies include uncontrolled, feasibility studies of short duration, and there is insufficient data to assess whether ingestion event sensors result in an improvement in net health outcomes. Large, well designed studies of sufficient duration are needed to adequately demonstrate clinical utility.

Background/Overview

Lack of medication adherence in individuals with communicable disease poses a threat to public health and noncompliance with chronic health treatment places a burden on the US healthcare system. Numerous interventions to help improve medication adherence in individuals with chronic disease have been attempted, and vary in their approaches, reliability, and demonstrated clinical utility. Ingestion event monitors hold the potential to allow providers to monitor medication adherence in real-time, without direct observation, enhancing targeted education and medical decision making. Ingestible sensors are swallowed along with an oral medication, allowing practitioners to monitor medication adherence. Currently available sensors are activated by contact with stomach contents; a signal is then transmitted to an exterior sensor worn by the individual. Once the outer capsule has dissolved, the sensor is excreted through the individual's gastrointestinal tract. Information regarding presence of the targeted medication is forwarded to an

application on the individual's mobile device and is uploaded to a portal for monitoring by medical professionals. The expectation of IEM use is that one sensor is ingested with each dose of the medication that requires monitoring. Each sensor has a unique identifier allowing providers to identify doses and times of ingestions and different medications if more than one sensor is ingested simultaneously.

There are currently two generalized (not medication-specific) ingestion event monitors on the market; both received clearance for marketing by the U.S. Food and Drug Administration (FDA). Proteus received FDA 510(k) approval in 2015 for the Digital Health Feedback Device. The device was approved with the intention to log ambulatory physiological and behavioral metrics including heart rate, activity, body position, and time-stamped events signaled by the ingestible sensor. The device allows for data collection to be unattended by healthcare personnel for clinical and research applications. In 2019, the FDA granted 510(k) clearance for the ID-Cap system with the intention to log, track, and also trend ingestion times allowing for unattended data collection and adherence monitoring.

Coding

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

When services are also Investigational and Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
99199	**Unlisted special service, procedure or report [when specified as an ingestion event monitor, for example, ID-CAP System or Discover]**
HCPCS	
A9279	**Monitoring feature/device, stand-alone or integrated, any type, includes all accessories, components and electronics, not otherwise classified [when specified as an ingestion event monitor, for example, ID-CAP System or Discover]**

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ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. **Browne SH, Umlauf A, Tucker AJ, et al. Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: a randomized controlled trial. PLoS Med. 2019; 16(10). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6777756/. Accessed on April 09, 2020.**
2. **DiCarlo LA, Weinstein RL, Morimoto CB, et al. Patient-centered home care using digital medicine and telemetric data for hypertension: feasibility and acceptability of objective ambulatory assessment. J Clin Hypertens (Greenwich). 2016; 18(9):901-906.**
3. **Eisenberger U, Wüthrich RP, Bock A, et al. Medication adherence assessment: high accuracy of the new Ingestible Sensor System in kidney transplants. Transplantation. 2013; 96(3):245-250.**
4. **Flores GP, Peace B, Carnes TC, et al. Performance, reliability, usability, and safety of the ID-Cap system for ingestion event monitoring in healthy volunteers: a pilot study. Innov Clin Neurosci. 2016; 13(9-10):12-19.**
5. **Frias J, Virdi N, Raja P, et al. Effectiveness of digital medicines to improve clinical outcomes in patients with uncontrolled hypertension and type 2 diabetes: prospective, open-label, cluster-randomized pilot clinical trial. J Med Internet Res. 2017; 19(7):e246. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5527253/. Accessed on April 09, 2020.**

Government Agency, Medical Society, and Other Authoritative Publications:

1. **U.S. Food and Drug Administration. 510(k) Premarket Notification Database. ID-Cap System. No. K183052. Gainesville, FL: FDA. December 06, 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K183052.pdf. Accessed on April 09, 2020.**
2. **U.S. Food and Drug Administration. 510(k) Premarket Notification Database. Proteus Digital Health Feedback Device. No. K150494. Redwood, CA: FDA. June 27, 2015. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf15/K150494.pdf. Accessed on April 09, 2020.**

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ID-Cap App
ID-Cap Dashboard
ID-Cap System
ID-Capsule
ID-Tag™
Proteus Discover
Proteus Discover App
Proteus Discover Portal

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	05/14/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

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