ITCA 650

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Introduction

In November 2016, Intarcia Therapeutics, Inc., submitted a new drug application for ITCA 650, the first implanted, injection-free glucagon-like peptide 1 (GLP-1) receptor agonist delivery device, which dispenses exenatide through an osmotic mini-pump for up to 1 year (1).

Indications

ITCA 650 will be used for patients with type 2 diabetes who have inadequate glycemic control from diet, exercise, and other antidiabetic medications. ITCA 650 has been shown to reduce body weight in addition to improving glycemic control (2).

Limitations of Use

Placement, replacement, and removal of the ITCA 650 osmotic mini-pump requires a minimally invasive subcutaneous surgical procedure by a trained health care provider (HCP) during an office visit (3). The device also requires surgical removal or replacement.

Mechanism of Action and Dosage

ITCA 650 provides continuous subcutaneous delivery of exenatide via an osmotic mini-pump surgically placed under the skin. This delivery system allows for the stabilization of proteins, peptides, antibody fragments, and other highly potent small molecules at or above human body temperatures for up to 3 years or more (4).

Exenatide, the GLP-1 receptor agonist delivered via the ITCA 650 device, improves glucose homeostasis through action in the kidneys, muscles, brain, pancreas, and elsewhere and is effective at maintaining glycemic control (5,6). Upon FDA approval, the ITCA 650 mini-pump likely would be made available in a 20 µg/day 3-month introductory dose, intended to be followed by a 60 µg/day 6-month maintenance dose (1).

Potential Advantages

GLP-1 receptor agonists have previously demonstrated effectiveness in improving glycemic control and reducing weight in patients with type 2 diabetes. ITCA 650 provides an alternative option for patients who struggle with medication adherence and the daily or weekly injections required by current GLP-1 receptor agonist options. After completing a 24-week trial of ITCA 650, 85% of eligible participants elected to continue in an optional 24-week extension phase of product use (2). These results indicate tolerability of the product and patient preference. Additionally, insurance companies and other payers reimburse procedures to place, replace, and remove nonbiodegradable drug delivery systems, reducing direct patient costs (7).

Potential Disadvantages

The ITCA 650 device requires surgical implantation by a specially trained HCP. The device must be replaced or removed after 12 months of use (3). In a 4-week study to evaluate tolerability of the ITCA 650, the most common adverse events included nausea (41%), decreased appetite

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(36%), vomiting (27%), early satiety (11%), and dizziness (9%) (8).

Cost

The subdermal implantation device will probably be set to a price of ~$10,000 (9).

Commentary

Surgical Implantation

ITCA 650 is a novel GLP-1 receptor agonist option because surgical implantation of the device replaces the need for daily or weekly injections. However, patients choosing the ITCA 650 will be required to have the device surgically placed by a trained HCP during an office visit. HCP training includes a brief online course followed by a hands-on training.

Each device is implanted in one of four abdominal quadrants, avoiding the midline inferior costal margin and the beltline (3). During the procedure, lidocaine is administered, and a 5-mm incision is made. Removal also entails creating a 5-mm incision, but when the device is being replaced, a new device can be inserted through the same incision.

As of June 2016, >18,000 procedures had been conducted to place, remove, or replace ITCA 650 devices, with a 99% success rate (3). Adverse events related to surgical implantation included temporary bleeding, discomfort, irritation, bruising, and pruritus but were reported to be consistent with the expected effects of minor surgical procedures (3).

Clinical Trials

Four global phase 3 clinical trials have been conducted with ITCA 650. The first was the FREEDOM-1 trial, a placebo-controlled, double-blind trial to determine the device's efficacy and safety. Four-hundred and fifty participants with type 2 diabetes were enrolled and received either ITCA 650 plus standard of care or placebo plus standard of care for 9 months. The ITCA 650 was shown to be superior in reducing A1C with both 40 and 60 µg/day doses of exenatide (10).

The FREEDOM-1 High Baseline study assessed A1C reduction among participants with a baseline A1C >10%. This 9-month, open-label study of 75 participants demonstrated sustained mean reduction in A1C of 3.4% from a mean baseline A1C of 10.8% (10).

The FREEDOM-2 trial compared ITCA 650 to sitagliptin and assessed reduction in weight and A1C in 500 participants with type 2 diabetes who had not achieved glycemic control on metformin. This 12-month, active comparator–controlled, double-blind, double-dummy study showed that participants receiving the ITCA 650 experienced a nearly twofold reduction in A1C (–1.5 vs. –0.8%, P <0.001) and a threefold reduction in weight (–4.0 kg [8.8 lb] vs. –1.3 kg [2.8 lb], P <0.001) compared to the sitagliptin arm (11).

The fourth and final phase 3 clinical trial was FREEDOM-CVO, a placebo-controlled cardiovascular outcomes trial with 4,000 participants taking a variety of antidiabetic medications (12). This trial was designed to meet the pre-approval safety assessment requirements set out in the U.S. Food and Drug Administration (FDA) guidance on evaluating cardiovascular risk for new therapies to treat type 2 diabetes (13). Participants were ≥40 years of age, had an A1C >6.5%, and had a history of coronary, cerebrovascular, or peripheral artery disease or multiple cardiovascular risk factors (12). The primary outcome measures were time to first occurrence of any event included in the major adverse cardiovascular events composite endpoint, which included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization due to unstable angina (14). The study met primary and secondary endpoints by demonstrating FDA-required pre-approval noninferiority for cardiovascular safety (12).

Clinical Implications

The clinical impact of the ITCA 650 device could be substantial. Poor adherence rate with pills and injections in type 2 diabetes accounts for a 75% reduced efficacy between real-world patients and those involved in clinical trials (15). Adherence can affect glycemic goals for a vast majority of patients with type 2 diabetes. Because this product would not require patient adherence and has been proven to reduce A1C and weight, its clinical impact could be significant.

The release date of the ITCA 650 will be contingent upon satisfaction of a Complete Response Letter issued by the FDA (16). Intarcia does not expect that new trials will be needed to satisfy FDA requests, and with transparent guidance provided by the agency, Intarcia's ITCA 650 is on a clear path toward release (16). If the ITCA 650 is processed via a Class 2 resubmission, review of an original application can be done in 6 months or less (17).

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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