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Turning the Tide with Tzield (teplizumab-mzwv): A Novel Agent for Delaying Type 1 Diabetes Onset

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According to the Centers for Disease Control (CDC), and estimated 37.3 million people (11.3%) of the United States population have diabetes mellitus, with of 23% of those going undiagnosed.[1] Of the patients diagnosed, 5.7% had type 1 diabetes mellitus (T1DM).[1] Type 1 diabetes mellitus, often referred to as juvenile diabetes, is caused by immune destruction of pancreas beta cells, resulting in the absence of insulin production and need for exogenous insulin administration.[2] This differs from type 2 diabetes (T2DM), when the body becomes resistant to natural insulin production over a prolonged period of time and poor lifestyle habits.[2]

As research continues to determine the potential genetic link to T1DM diagnosis, recent studies indicate that genetically susceptible individuals (defined as first-degree family members of a diagnosed T1DM patient) may be screened for autoantibodies and staged prior to clinical symptom presentation of T1DM diagnosis.[3] Stages are numerically designated 1 through 3 and classify individuals based on the prevalence of autoantibodies and associated presence of hyperglycemia symptoms as staging progresses (**Figure 1**).[4] First degree relatives of individuals with T1DM are considered high-risk for the development of T1DM and are recommended to be screened for early detection and staging.[3] Use of early staging and screening for autoantibodies (proinsulin, glutamic acid decarboxylase-65 (GAD), insulinoma-associated antigen-2 (IA-2), and zinc transporter 8 (ZnT8)) has led to the development of new medication targets and the potential to delay onset of disease.[4]

Individuals with Stage 1 T1DM are characterized by the appearance of two or more differing islet autoantibodies indicating beta-cell autoimmunity but are normoglycemic and asymptomatic.[3] Stage 2 includes a loss of beta cell mass leading to glucose intolerance. In the majority of patients this loss in beta cell mass happens after 5 years from the onset of C -peptide decline.[4] Clinical measurements of the progression to Stage 2 include: impaired fasting glucose of >100 mg/dL (>5.6 mmol/L), impaired glucose tolerance with 2-hour plasma glucose from a 75-gram oral glucose tolerance test (OGTT) of ≥140 mg/dL (≥7.8 mmol/L), high glucose levels at intermediate time points on OGTT (30, 60, 90 min) levels of ≥200 mg/dL [≥11.1 mmol/L]), and/or HbA1c ≥5.7% (≥39 mmol/mol).[3] For patient that screen positive for Stage 1, repeat metabolic testing is recommended every 6-12 months due to rapid decrease in beta cell function. Individuals with Stage 1 and Stage 2 generally have a normal C-peptide (marker of insulin secretion), with observed sharp decline 6 months prior to progression into Stage 3 T1DM.[3]

Stage 3 T1DM occurs in the presence of two or more autoantibodies with hyperglycemia symptoms, including polyuria, polydipsia, polyphagia, weight loss and fatigue.[3] Unfortunately, this stage may manifest as diabetic ketoacidosis (DKA), a condition occurring when the body cannot produce enough insulin to cover elevated serum glucose levels.[5] Oftentimes when individuals experience DKA, hospitalization is required to prevent end organ damage.[5] In addition, the presentation of DKA at Stage 3 T1DM onset is associated with increased mortality and lower residual beta-cell function, ultimately indicating worse metabolic control, higher insulin requirements, and adverse short-term neurocognitive outcomes.[4]

Overall, the use of staging in individuals with a genetic link to T1DM development has led to better health outcomes.[4] In addition to staging for individuals at high risk for T1DM diagnosis, researchers have also begun evaluation of the genetic link to T1DM via targeted immunosuppression. At the core of T1DM diagnosis, the immune system is disequilibrated with autoreactive T-cells.[6] This imbalance leads to an autoimmune response and eventual destruction of beta cells. Cytokines help to regulate the immune system from disequilibrium by binding to receptors on immune cells (such as CD3/4) and triggering signaling pathways for T cell differentiation, for example through Fc receptors.[6]

One promising new type of therapy is though the activation of the Fc receptor with a nonbinding anti-CD3 monoclonal antibody, teplizumab. The Fc receptor, with associated presentation of antigens on the beta cell, serves as an important step in the development of T-cell mediated T1DM.[7] As of March 2009, over 450 individuals with T1DM have been treated with teplizumab throughout seven ongoing, or recently completed, clinical studies.[8-14] Two clinical trials proving safety and efficacy of teplizumab have been completed in participants with recent Stage 3 T1DM as well as four additional ongoing clinical trials evaluating the preservation of beta cell function in those diagnosed T1DM.[8-14] While preliminary results from these studies have shown that teplizumab reduces the loss of beta-cell function up to seven years after diagnosis, the utility of teplizumab in altering the progression of T1DM during Stages 1 through 3 has not yet been demonstrated.[8-15]

In November 2022, the United States Food and Drug Administration (FDA) approved the novel drug Tzield® (teplizumab) for the delay of onset of T1DM in adults with Stage 3 T1DM and pediatric patients 8 years and older with Stage 2 T1DM based on new clinical data published by Herold et al. in 2019.[15] This manuscript aims to explore the expanded clinical use of teplizumab, its pharmacological profile, and distinctive properties leading to the first FDA-approved medication in its class for delaying the onset of T1DM.

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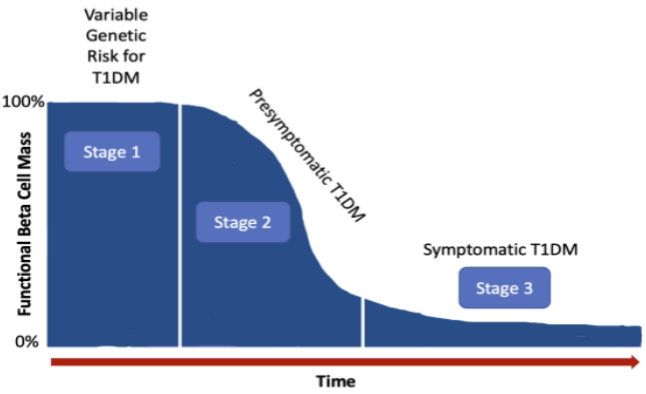
Figure 1 | Early Stages of Type 1 Diabetes[4]



Mechanism of Action

Teplizumab is a CD3-directed monoclonal antibody that binds to CD3 (a cell surface antigen on T lymphocytes) via the Fc receptor.[16] Clinical studies have shown that teplizumab binds to CD3 molecules on the surface of both CD4+ and CD8+ T cells during treatment, with internalization of the teplizumab/CD3 complex from the surface of T cells.[8-10] This internalization may activate partial agonistic signaling via the Fc receptor and deactivation of pancreatic beta cell T lymphocytes, although the complete mechanism is unclear. Use of teplizumab has been linked to an increase in the proportion of regulatory T cells and CD8+ T cells in peripheral blood.[16] Ultimately, deactivation of beta cell T lymphocytes hinders autoimmune-mediated destruction of beta cells extending the life of the innate pancreas and insulin secretion.[16]

Pharmacodynamics & Pharmacokinetics

Steady state concentrations of teplizumab are not expected to be achieved during the 14-day course of medication therapy (see Dosage, Administration, & Cost) and should not be used as a marker of appropriate bodily response.[16] The central volume of distribution (Vd) of teplizumab was 2.27 L in a 60 kg subject with notable saturable binding and elimination (mean half-life 4.5 days; clearance 2.7 L/day).[16] Teplizumab is eliminated through catabolic metabolism with no clinically significant differences observed based on age (8 to 35 years old), biologic sex, or racial groups (White and Asians studied) as it relates to pharmacokinetics. Body surface area-based dosing normalized the exposure to drug therapy across body weight.[16]

Pharmacodynamic effects include lymphopenia in the absence of depletion of T cells with a nadir on the fifth day of dosing. The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of teplizumab have not been fully characterized.[11]

Clinical Trial: Study TN-10

The FDA approval of Tzield® for the delay in onset of clinical T1DM was based on data from the TN-10 study published by Herold et al in 2019.[15] This study was a phase II, multicentered, randomized controlled trial conducted from July 2011 to November 2018 for patients to receive either teplizumab or placebo. Patients were then stratified according to site, age (<18 years or >18 years) and second OGTT results (impaired vs. normal vs. diabetes). All treatment group assignments were masked, and participants received a 14-day treatment of drug or saline placebo via intravenous infusion. Teplizumab was given at a dose of 51 µg/m2 of body-surface area on day 0, a dose of 103 µg/m2 on day 1, a dose of 207 µg/m2 on day 2, and a dose of 413 µg/m2 on day 3, followed by a dose of 826 µg/m2 on each of days 4 through 13.[15]

Participants were identified for study inclusion through the TrialNet Natural History Study, a previous cohort study designed to identify potential trial subjects with natural history information regarding pre-type 1 diabetes.[17] Eligible participants were included if a first degree relative of patients with T1DM, age 8 – 45 years old, and had two or more diabetes-related autoantibodies detected in two serum samples within 6 months of randomization.[15] Second or third degree relatives were also included, but must be between ages of 8 – 20 years old. Evaluated autoantibodies included micro insulin (mIAA), GAD-65, and IA-2. Islet cell (ICA) and ZnT8 autoantibodies were measured if at least 1 other antibody tested positive. In addition, participants must have demonstrated evidence of glucose intolerance during an OGTT within 52 days prior to enrollment. Glucose intolerance was defined as a fasting glucose level of 110 to 125 mg/dL (6.1 to 6.9 mmol/L), a 2-hour postprandial plasma glucose level of at least 140 mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L), or an intervening postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg/dL on two separate occasions.[15] Participants were excluded if diagnosed previously with Stage 3 T1DM, found to have abnormal blood counts (such as lymphopenia, neutropenia, thrombocytopenia, and anemia), abnormal laboratory chemical values (total bilirubin, AST, or ALT >1.5 upper limit of normal), or other clinically relevant medical histories.[15]

The primary objective of the study was to determine if treatment with teplizumab results in a delay of T1DM. This endpoint was measured by the time from randomization to the time of clinical diagnosis of T1DM.[15] Scheduled OGTT tests were performed 3 months and 6 months after the treatment infusion and every 6 months thereafter. Random screening glucose levels were evaluated at 3-month intervals, and an OGTT test was performed if the random glucose level was higher than 200 mg/dL (11.1 mmol/L) in association with standardized symptoms of diabetes. Secondary endpoints to include analyses of C-peptide responses and other measures from the OGTT pertaining to safety and tolerability with comparison of teplizumab to placebo.

Statistical analysis consisted of the cumulative incidence of diabetes diagnosis within each group over time after randomization and was estimated in a Kaplan–Meier analysis with the difference between the treatment groups (6-month-interval cumulative-incidence functions) estimated as a hazard ratio. Endpoints were evaluated with the use of a likelihood ratio test based on the Cox proportional-hazards model. Due to slower than expected rates of enrollment, the study protocol was modified to detect a 60% lower risk in the teplizumab group than in the placebo group with 80% statistical power at an alpha level of 0.025 (one-sided).[15] Clinically this set the goal of enrolling at least 71 participants and following them until 40 participants had received a diagnosis of T1DM. Safety and efficacy data was evaluated routinely by an independent data and safety monitoring board. Data was analyzed with an intent-to-treat protocol.[15]

The study included a total of 112 participants who were screened for eligibility, with a total of 76 participants meeting inclusion criteria (44 in the teplizumab group and 32 in the placebo). Treatment groups were similar in baseline characteristics with the majority less than 18 years old, white, and more than half were siblings of patients with T1DM. In total, 93% of participants in the teplizumab group and 88% in the placebo group completed the 14-day course of treatment. The median total dose of teplizumab administered was 9.14 mg/m2. Three participants in the teplizumab group and four participants in the placebo group did not complete the trial regimen due to concerning laboratory abnormalities, inability to achieve intravenous access, or rash. The median follow-up duration was 745 days (ranging from 74 to 2683) with the duration of follow-up more than 3 years in 57 participants (75%). At conclusion of the trial, Stage 3 T1DM was diagnosed in 42 trial participants (55%).[15]

Primary endpoint results indicate treatment with teplizumab delayed the time to diagnosis of T1DM, with the median time to diagnosis at 48.4 months in the teplizumab group and 24.4 months in the placebo group (hazard ratio, 0.41; 95% confidence interval, 0.22 to 0.78; two-sided P=0.006). The annualized rates of diagnosis of T1DM were 14.9% per year and 35.9% per year in the teplizumab group and the placebo group, respectively. The largest effect of teplizumab treatment on Stage 3 T1DM diagnosis was found within the first year of randomization in 3 out of 44 participants (7%) in the teplizumab group, in contrast to 14 out of 32 participants (44%) in the placebo group (unadjusted hazard ratio, 0.13; 95% CI 0.05 to 0.34), although not statistically significant.[15]

Results found teplizumab treatment to be associated with both clinically and statistically relevant adverse events. Findings concerning for a lymphocyte count reduction to a nadir on day 5 of treatment (total decrease, 72.3%; interquartile range, 82.1 to 68.4; P<0.001) in addition to a rash occurring in 16 (36%) of participants who received teplizumab.[15] Notably for 85% of participants with significant lymphopenia with teplizumab initiation, circulating lymphocytes returned to >80% of baseline within 2 months of treatment. Participants experiencing rash were observed to have a macular rash on the face, neck, truck, and extremities. Most cases resolved spontaneously with supportive care, but often resulted in peeling of the skin. Notable biopsy results consistent with eczematous dermatitis, and resolution occurred with teplizumab dose reduction and supportive care. The rates of infection were similar in the two treatment groups, but anti-CD3 monoclonal antibody treatment was associated with Epstein–Barr virus (EBV) and cytomegalovirus (CMV) reactivation. No participants died secondary to EBV or CMV reactivation.[15]

Subgroup analysis evaluated the effects of teplizumab based on age, HLA gene type, pretreatment C-peptide and glucose levels, and autoantibodies. Among the 43 participants in the teplizumab group, 21 (49%) had HLA-DR3 and 28 (65%) had HLA-DR4 major histocompatibility complex (MHC) molecules. The presence of HLA-DR4 and absence of HLA-DR3 were associated with more robust responses to teplizumab (hazard ratio, 0.20 [95% CI, 0.09 to 0.45] and 0.18 [95% CI, 0.07 to 0.45], respectively). In addition, the response to teplizumab as compared with placebo was greater among participants without anti–zinc transporter 8 (ZnT8) antibodies than among those with these antibodies (hazard ratio, 0.07; 95% CI, 0.02 to 0.26), although not significant. The response to teplizumab was also greater among participants whose C-peptide values to the OGTT test at baseline was below the median than among those whose values were above the median (hazard ratio, 0.19; 95% CI, 0.08 to 0.47). In addition, females responded better to teplizumab treatment overall.[15]

In this phase II trial, authors found a single 14-day course of teplizumab significantly slowed progression of clinical Stage 3 T1DM in high-risk, nondiabetic relatives of patients with diagnosed T1DM. The median delay in the diagnosis was ~2 years, with the percentage of diabetes-free patients in the teplizumab group (57%) double that of the placebo (28%).[15] Associated safety analyses revealed significant, yet expected, adverse events of rash and transient lymphopenia in both children and adults. In conclusion, this study supports a 14-day course of treatment with teplizumab to delay the onset of Stage 3 T1DM in adults with Stage 3 T1DM and pediatric patients 8 years and older with Stage 2 T1DM.[15]

Adverse Effects

Cytokine Release Syndrome (CRS)

In clinical trials, CRS was reported in 5% of teplizumab-treated patients compared to 0.8% of placebo-treated patients during the treatment period and extending 28 days after the last study drug administration.[8-15] Manifestations of CRS symptoms typically occurred during the first 5 days of teplizumab treatment and were mitigated with premedication of antipyretics, antihistamines and/or antiemetics prior to teplizumab treatment. All study participants were administered ibuprofen and an antihistamine prophylactically prior to infusion with teplizumab or placebo during the first 5 days of treatment.[15]

In addition, routine monitoring of liver enzymes is recommended during treatment and discontinuation of treatment in patients who developed elevated ALT or AST more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN occurred during the treatment study.[15,16] If severe CRS develops, discussion with the patient regarding continuation of therapy is appropriate. Consider temporarily pausing dosing for 1-2 days (and administer the remaining doses to complete the full 14-day course on consecutive days) or discontinuing treatment.[16]

Serious Infections

Bacterial and viral infections occurred in teplizumab-treated patients. In clinical trials, patients had a higher rate of serious infections (3.5%) than placebo-treated patients (2%), including gastroenteritis, cellulitis, pneumonia, abscess, sepsis.[8-15] Participants were instructed not to use oral, inhaled, or nasal corticosteroids or other immunosuppressive drugs during this trial to reduce infection risk and prevent impact on progression to diabetes.[15]

Use of teplizumab is not recommended in patients with an active serious infection or chronic infection other than localized skin infections.[16] Continued monitoring of patients for signs and symptoms of infection during and after treatment is recommended. If serious infection develops, treat appropriately, and discontinuation of teplizumab therapy is advised.[16]

Lymphopenia

In clinical trials, 78% of teplizumab-treated patients developed lymphopenia compared to 11% of placebo-treated patients.[8-15] For most patients who experienced lymphopenia, lymphocyte levels began to recover after the fifth day of treatment and returned to pre-treatment values within two weeks after treatment completion and without dose interruption.[16] Severe lymphopenia (<500 cells/mcL) lasting one week or longer occurred in 0.9% of patients, and 0.5% of patients discontinued teplizumab due to lymphopenia.[8-15] Recommended monitoring of white blood cell counts during the treatment period is advised. If prolonged severe lymphopenia develops, discontinue teplizumab immediately.[16]

Hypersensitivity Reactions

Acute hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm have occurred.[8-15] If severe hypersensitivity reactions occur, discontinue use of teplizumab and treat promptly. Premedication prior to each teplizumab infusion for the first 5 days of dosing with: a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, an antihistamine, and/or an antiemetic is recommended.[16]

Vaccinations

The safety of immunization with live-attenuated vaccines in patients treated with teplizumab has not been studied.[16] Current trial criteria excluded participants if having received a live virus vaccine within 8 weeks of randomization and 4 weeks for a killed vaccine.[15] Additionally, treatment may interfere with the immune response to vaccination and decrease vaccine efficacy. Patients should be advised to administer all age-appropriate vaccinations prior to starting teplizumab.[16] In addition, inactivated or mRNA vaccinations are not recommended within the 2 weeks prior to, during, or 6 weeks after completion of treatment. In contrast, live-attenuated vaccinations are not recommended within the 8 weeks prior to, during, or up to 1 year after treatment completion.[16]

Safety & Contraindications

Prior to initiating teplizumab, providers should obtain a complete blood count and liver enzyme tests to establish baseline labs. Use of teplizumab is not recommended in patients with: lymphocyte count less than 1,000 lymphocytes/mcL, hemoglobin less than 10 g/dL, platelet count less than 150,000 platelets/mcL, absolute neutrophil count less than 1,500 neutrophils/mcL, elevated ALT or AST greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN, laboratory or clinical evidence of acute infection with EBV or CMV, or an active serious infection or chronic active infection other than localized skin infections.[16]

No current contraindications exist for use of treatment, but no long-term studies have been performed to assess the carcinogenic or mutagenic potential of teplizumab.[16] In addition, no studies have evaluated the risk of infection with teplizumab while using chronic corticosteroids or other monoclonal antibody treatment and should be cautioned.[16]

Dosage, Administration, & Cost

Tzield®(teplizumab) injection is supplied as a sterile, preservative-free, clear, and colorless solution in a 2 mg/2 mL single-dose vial for intravenous use.[16] Vials should be stored at 2°C to 8°C (36°F to 46°F) in the original carton and protected from light prior to use. Do not freeze or shake the vials. Medication must be diluted with 0.9% sodium chloride prior to use per directions on the package insert. If not used immediately, store the diluted solution at room temperature and complete the infusion within 4 hours from the start of preparation.[16]

The medication is administered by intravenous infusion over a mini-

mum of 30 minutes in duration, using body surface area-based dosing. Each dose is administered once daily for 14 consecutive days as follows: Day 1: 65 µg/m2, Day 2: 125 µg/m2, Day 3: 250 µg/m2, Day 4: 500 µg/m2, Days 5 through 14: 1,030 µg/m2. Do not administer two doses on the same day. If a planned infusion is missed, resume dosing by administering all remaining doses as planned in consecutive days to complete the 14-day treatment course.[16]

Teplizumab can only be ordered through the medication manufacturer, Provention Bio Pharmaceuticals, at this time.[18] If providers want to start a patient on teplizumab, the patient must fill out Provention Bio COMPASS forms with a submitted active prescription. Once acquired, the manufacturer will contact the patient regarding cost of the treatment plan and arrange for local infusion center training and administration. Currently pricing for teplizumab (as of May 2023) is unavailable for public review at this time, but in November 2022 the manufacturer estimated cost at $13,850 per vial and a 14-day course at $193,900 wholesale price per consumer.[19] Insurance coverage is limited, but patient financial assistance is available for those with insufficient copay coverage on insurance or those uninsured.[18]

Special populations

There is limited to no data on teplizumab use in pregnancy or lactation.16 Clinical trials have excluded participants who are currently pregnant and required proof of a negative pregnancy test prior to randomization.[15] Monoclonal antibodies can be actively transported across the placenta, and teplizumab may cause immunosuppression in utero.[16] To minimize exposure to a fetus, avoid use during pregnancy and at least 30 days (6 half-lives) prior to planned pregnancy. It is advised that lactating women should interrupt breastfeeding, pump, and discard breast milk during treatment and for 20 days after teplizumab administration for safety.[16]

The safety and effectiveness of teplizumab to delay the onset of Stage 3 T1DM has been established in pediatric patients 8 years of age and older with Stage 2 T1DM.[15] Adverse reactions observed in pediatric patients 8 years of age and older who received teplizumab were consistent with those reported in adult patients.[16] The safety and effectiveness of teplizumab has not been established in pediatric patients younger than 8 years of age, caution is advised.[16]

Stage 2 T1DM is largely a condition that occurs in pediatric and younger adult patients.[4] Clinical studies to delay the onset of Stage 3 T1DM did not include patients 65 years of age and older.[15] Use is cautioned in patients over the age of 65 years due to limitations with study data.[16]

Clinical Implications

In the Study TN-10 trial, a single course of 14-day teplizumab was found to significantly delay onset of T1DM in relatives of patients with diagnosed T1DM with additional risk factors. Study participants on teplizumab were found to have a delayed onset of T1DM by a median of 2 years, with the percentage of diabetes-free persons in the teplizumab group (57%) double that in the placebo group (28%). The largest effect of teplizumab treatment on T1DM onset was noted within the first year of randomization and secondary endpoint analyses may indicate the importance in selection, and screening, of autoantibodies for early detection. Overall, study results support that T1DM is a chronic T-cell–mediated disease and suggests that immunomodulation before the development of clinical disease may be useful to slow T1DM onset.[15]

While study findings were significant, the trial had limitations that should be considered prior to generalization. The cohort size was relatively small (n=76), with a power of 80% requiring a minimum of 71 participants. To meet this statistical power, at least 40 participants needed to be diagnosed Stage 3 T1DM. At conclusion of the trial, a total of 42 participants were clinically diagnosed Stage 3 T1DM; therefore, the trial was adequately powered despite rolling admission based on inclusion criteria. All included participants were relatives of patients with known T1DM, and findings may not be applicable to persons who do not have first-degree relatives with T1DM diagnosis or in whom this aspect of family history is unknown.[15] Current literature does not discuss the use of teplizumab for patients without known family history of T1DM but is an area of research moving forward.

In addition, the trial population was largely made up of non-Hispanic white participants making study findings hard to extrapolate to other ethnicgroups.[15] According to the CDC, between 2011 to 2015 Hispanic children and adolescents had the largest increase in new T1DM diagnosis compared to other ethnicity groups, followed by non-Hispanic Asian or Pacific Islander children and adolescents.[20] This statistic emphasizes the need to include a wide variety of ethnicities in study design in order to extrapolate data to other populations. In addition, teplizumab, based on study protocol, was administered for one 14-day course. Repeat dosing strategies have not been studied, which may be of interest for future avenues of research..[15]

Furthermore, use of teplizumab as a monoclonal antibody comes with associated risks, including immunomodulatory rejection or the potential development of antibodies to the monoclonal antibody teplizumab, which may be a concern.[15] Hansel et al. details the potential for great successes in precision immunomodulation as well as risk with use of monoclonal antibodies to date, including similar adverse effects prevalent with teplizumab.[21] Notable reactions, including the cytokine release syndrome and increased risk of infection, are frequent in many other biologic agents at market, including one similar to teplizumab, such as muromonab-CD3. Muromonab-CD3 is the closest in structure and cellular target to teplizumab for comparison and functions to suppress renal allograft rejection. In contrast to teplizumab, muromonab-CD3 is a mouse antibody targeted against human CD3, but also can cause CRS and severe influenza-like syndrome.[21] Researchers have developed an ongoing register of biologics to monitor for safety with continued use, and anticipate adverse reactions (along with subsequent preventative care) based on previously approved agents.[21] In previous trials of teplizumab-treated participants antidrug antibodies were noted in approximately 20% to 55% after the initial treatment course, but the effects on the immunologic or clinical outcomes are not clear.[8-14] Further testing, and development of specialized assays is needed to determine such outcomes as it relates to cellular antibody effects.[15]

Lastly, the cost of the teplizumab infusion over the 14 days of treatment totals over $190,000 and further limits patient access, regardless of insurance coverage.[18] Combined with the outcome of delaying onset of T1DM by ~2 years, but not preventing the disease altogether, patients may not feel the cost is worth the benefit. This is largely dependent on patient specifics, both genetically and socioeconomically. In contrast, slowing the onset of T1DM may be extremely beneficial in these patients with worse outcomes linked to an early diagnosis of T1DM, including poorer metabolic control and higher insulin requirements long term. Early discussion and screening may be of benefit to a patient at risk for developing T1DM, and data with teplizumab supports this discussion. In addition, use of non-stimulating beta cell medications or medications proven to preserve beta cell function, such as incretin memetics and verapamil, should also be mainstay medication therapy in patients unable to afford teplizumab.[15,22]

For those with a family history or with a first-degree relative with T1DM, patients should discuss the potential for autoantibody testing (and associated costs) with a clinician. While these tests are available, ability for completion may be limited based on patient's family history, insurance, location and financial burden. While this discussion is started within the primary care office, a referral to an endocrinologist may be warranted prior to determining teplizumab use.

Conclusion

The FDA-approval of the non-binding CD3-directed monoclonal antibody Tzield® (teplizumab), has shown to delay the onset of clinical T1DM in high-risk patients.[15] The effects of teplizumab were greatest in the first 3 years after administration and slowed disease onset by ~2 years. Notably, the response to teplizumab was greatest among participants with C-peptide responses that were below the median, related to an individual with T1DM, and had two or greater autoantibodies present at time of randomization.[15] While little data is known about repeat dosing,

antidrug antibody response, and associated costs, this medical breakthrough is the first monoclonal antibody to target T1DM and provides hope to patients with a family history of type 1 diabetes or those at high-risk for disease development. Clinically, if patients are genetically susceptible to T1DM development, discussion with a primary care physician regarding autoantibody screening is advised. If screening suggests potential for future T1DM development, referral to a specialist to discuss the use of teplizumab is encouraged to evaluate risks, testing, costs, and adverse effects of medication use. Study data suggests that responses to teplizumab differ based on characteristics of the participants and should be discussed thoroughly prior to treatment.

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Personalized Medicine Corner

Updates to Sertraline Dosing Recommendations Based on Pharmacogenomics

Eda Eken, PharmD

Sertraline (Zoloft®) is a selective serotonin reuptake inhibitor (SSRI) that has demonstrated effectiveness and safety in treating several psychiatric disorders including major depressive disorder (MDD), panic, generalized and social anxiety disorders as well as obsessive compulsive disorder (OCD) in the dose range of 50–200 mg daily.[1,2] It has similar effectiveness to other SSRIs and the most common adverse effects include weight gain, insomnia, headache, GI dysfunction, and sexual dysfunction.

SSRIs increase serotonergic activity by decreasing presynaptic serotonin reuptake. Sertraline is hepatically metabolized to its only active metabolite, desmethylsertraline, primarily by CYP2B6, with minor metabolism via CYP2C19, CYP3A4 and CYP2C9.[3,4] Of these enzymes, only *CYP2C19* and *CYP2B6* genetic variations have sufficient evidence demonstrating an association with sertraline exposure.[5] Although active, desmethylsertraline has not shown a notable clinical effect, as it exhibits ~20-fold less potency as a serotonin reuptake inhibitor than sertraline.[6]

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published SSRI clinical practice guidelines to help guide dosing based on pharmacogenomic (PGx) test results.[7,8] In regards to sertraline, CPIC conducted new evidence reviews and in 2023 updated guidelines to include new PGx-guided dosing recommendations based on *CYP2B6* alone, *CYP2B6* combined with *CYP2C19*, as well as updated recommendations based on *CYP2C19* alone.

Interpretation of Pharmacogenetic Results

CYP2C19

CYP2C19 variants have shown to have the greatest impact on sertraline pharmacokinetics (PK), as summarized in **Table 1**. While the relationship between CYP2C19 no-function alleles (e.g., *2 and *3) and sertraline exposure/response has been demonstrated, the increased function (*17) allele has not been observed to greatly affect sertraline plasma concentrations.

CYP2B6

CYP2B6 is also highly polymorphic with 38 variants currently defined by PharmVar.[9] Compared to patients carrying 2 normal function alleles (e.g., *1), those with 1-2 decreased function (e.g., *6 and *9) or no function (e.g., *18) alleles may have increased concentrations of sertraline[5] and decreased rate of desmethylsertraline formation;[10] and those with 1-2 increased function alleles (e.g., *4), may have decreased concentrations of sertraline. Phenotype translations based on diplotypes and influence on sertraline metabolism are shown in **Table 1**.

Therapeutic Recommendations

CYP2C19

Based on the updated CPIC SSRI guidelines, adjustments to sertraline dosing are not warranted for UMs or RMs. UMs previously had a recommendation to avoid sertraline and consider an alternative, however, due to the small increase in sertraline metabolism and lack of clinical outcomes, there is now no recommendation to alter dosing. Of note, RMs and NMs were previously grouped into extensive metabolizer category, now distinct recom-

Table 1 | CYP2C19 and CYP2B6 Single Gene Dosing Recommendations for Sertraline[7,8]

Gene	Phenotype	Diplotype Examples	Implication on Sertraline Metabolism	2015 Recommendation[7]	2023 Recommendation[8]
CYP2C19	UM	*17/*17	Small increase in metabolism to less active compounds	Consider an alternative drug not predominantly metabolized by CYP2C19.	Initiate therapy with recommended starting dose
	RM	*1/*17	Small increase in metabolism to less active compounds	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose
	NM	*1/*1	Normal metabolism	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose
	IM	*1/*2, *1/*3, *2/*17	Decreased metabolism to less active compounds	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose. Consider a slower titration schedule & lower maintenance dose.
	PM	*2/*2, *3/*3	Very decreased metabolism to less active compounds. Higher plasma levels may increase risk of side effects.	Consider 50% reduction of recommended starting dose and titrate to response or select alternative not metabolized by CYP2C19.	Consider lower starting dose, slower titration schedule & 50% reduction of standard maintenance dose or select alternative not metabolized by CYP2C19.
CYP2B6	UM	*4/*4	Increased metabolism to less active compounds	N/A	Initiate therapy with recommended starting dose
	RM	*1/*4	Small increase in metabolism to less active compounds	N/A	Initiate therapy with recommended starting dose
	NM	*1/*1	Normal metabolism	N/A	Initiate therapy with recommended starting dose
	IM	*1/*6, *4/*6, *1/*9, *4/*9, *1/*18, *4/*18	Decreased metabolism to less active compounds	N/A	Initiate therapy with recommended starting dose. Consider a slower titration schedule & lower maintenance dose.
	PM	*6/*6, *6/*9, *9/*9, *6/*18, *18/*18	Very decreased metabolism to less active compounds. Higher plasma levels may increase risk of side effects.	N/A	Consider lower starting dose, slower titration schedule & 25% reduction of standard maintenance dose or select alternative not metabolized by CYP2B6.

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mendations exist for these phenotypes. Existing data do not support adjusting starting doses for IMs, but a slower titration and lower maintenance dose may be warranted due to reduced metabolism and risk for side effects. If sertraline is clinically indicated in PMs, dose adjustments (as described in **Table 1**) or selecting an alternative antidepressant not predominately metabolized by CYP2C19 should be considered to minimize unfavorable clinical outcomes (e.g., increased discontinuation and increased side effects).

CYP2B6

Recommendations for CYP2B6 UMs, RMs, NMs, and IMs are the same as CYP2C19 recommendations above. For PMs a lower starting dose, slower titration, and a 25% reduction of standard maintenance doses should be considered. Evidence supporting decreased metabolism in IMs and PMs are derived primarily from PK studies (see supplement **Table 3**), therefore CPIC has classified these recommendations are optional due to lack of clinical outcome data (e.g., toxicity).

Combined CYP2C19 and CYP2B6

Treatment modification to single gene (i.e., *CYP2B6* or *CYP2C19* alone) recommendations may be warranted given the combination of CYP2C19 and CYP2B6 phenotypes, as summarized in **Table 2**. Sertraline dosing recommendations for CYPC19/CYP2B6 are based on reported or calculated percentage differences in exposure compared to NMs (see supplement **Table 3**). For example, Parikh et al. identified 36% more patients with significantly decreased sertraline metabolism based on combined *CYP2C19/CYP2B6* results versus *CYP2C19* alone; consequently, those 36% were not considered for changes in sertraline therapy.[11] Additionally, Braten et al observed a 2.9-fold increase in sertraline serum concentrations in combined PMs (CYP2C19 + CYP2B6 PMs) vs combined NMs (CYP2B6 + CYP2C19 NMs); and 35.4% lower sertraline serum concentrations in combined UMs (CYP2B6 UMs/RMs + CYP2C19 UMs) vs combined NMs.[5] Overall concluding that individualized dosing based on combined CYP2C19/CYP2B6 genotype results may minimize over- or under-exposure of sertraline.

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Practical Application

EJ is a 62 yo male with PMH significant for depression and anxiety. He presents to his psychiatrist complaining of worsening symptoms (sad and feels worthless the whole time) despite taking escitalopram 20 mg daily. EJ underwent pharmacogenetic testing a year ago and his psychiatrist referred him to the PGx clinic to review his results and to provide the best recommendation to help control his depression and anxiety. EJ's psychiatrist plans on starting sertraline, what is the most appropriate recommendation based on the his pharmacogenetic result below?

His pharmacogenetic test results are as follows:

Gene	Genotype	Phenotype
CYP2C19	*1/*17	Rapid metabolizer (!)
CYP2B6	*6/*6	Poor metabolizer (!)
CYP2D6	*2/*2	Normal metabolizer

Recommendation

Based on CPIC's combined recommendation for CYP2B6 PM and CYP2C19 RM, sertraline may be initiated at recommended starting dose of 50 mg daily for MDD. Titrate to desired response and tolerability. Alternatively, consider a non-CYP2C19 SSRI (e.g., paroxetine, fluoxetine, fluvoxamine) OR a non-SSRI antidepressant (e.g., duloxetine, bupropion, venlafaxine) as clinically appropriate.

Table 2 | Combined CYP2C19 and CYP2B6 Dosing Recommendations for Sertraline[7]

Phenotype	CYP2B6 UM or RM	CYP2B6 NM or IM	CYP2B6 PM
CYP2C19 UM or RM	Initiate therapy with recommended starting dose. If no response to recommended maintenance dose, consider increasing dose or switching to an alternative non-CYP2C19 or CYP2B6 SSRI.[a]	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose.[b]
CYP2C19 NM	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose.	Consider lower starting dose, slower titration schedule & 25% reduction of standard maintenance dose or select an alternative non-CYP2B6 SSRI.[c]
CYP2C19 IM	Initiate therapy with recommended starting dose.	Initiate therapy with recommended starting dose. Consider a slower titration schedule & lower maintenance dose.	Consider lower starting dose, slower titration schedule & 50% reduction of standard maintenance dose.[a]
CYP2C19 PM	Consider lower starting dose, slower titration schedule & 50% reduction of standard maintenance dose or select an alternative non-CYP2C19 SSRI. [b]	Consider lower starting dose, slower titration schedule & 50% reduction of standard maintenance dose or select an alternative non-CYP2C19 SSRI. [b]	Select an alternative non-CYP2C19 or CYP2B6 SSRI.[a]

a. Differs from both CYP2C19 and CYP2B6 recommendations; b. Differs from CYP2B6 single gene recommendation; c. Differs from CYP2C19 single gene recommendation

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Clinical Conundrums

Expanded Coverage for Continuous Glucose Monitors (CGMs) for Medicare & Medicaid Patients

Christie Monahan, PharmD

Continuous glucose monitors (CGMs), have revolutionized the way patients and providers manage diabetes and has proven a helpful tool when making decisions regarding medication management.[1] CGMs provide patients with dynamic information about their blood glucose levels allowing the ability to easily perform insulin adjustments based on blood glucose and carbohydrate intake, leading to optimized medication use and improved HbgA1c control.[2,3] In addition, patients can view their blood glucose levels around the clock with real-time alerts for blood glucose outside of target range.[1] These alerts allow for prompt treatment of hypoglycemia to ensure safe use of insulin. On the other hand, hyperglycemia alerts can be adjusted based on patient goals and provider recommendations. Use of hyperglycemia alerts can also assist with patient adherence to medication therapy. Studies have showed use of CGM has decreased hospitalizations for diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome.[3,4] Use of CGM devices give patients the opportunity to take ownership and become a part of the shared decision-making team, ultimately leading to better healthcare outcomes and a strengthened relationship between the patient and provider.[5]

While patients find multiple benefits of CGM use, providers have also been able to utilize this technology to further assess patient blood glucose patterns, medication adherence and dosing regimens. A meta-analysis of 14 randomized controlled trials has found that patients using CGM, instead of fingerstick, have an average A1c reduction between -0.3 to -0.6% at 12 – 16 weeks.[6] Many healthcare facilities are integrating CGM use into clinic workflow to equip physicians with easy access to the Ambulatory Glucose Profile (AGP) reports in order to aid in clinical decision making and recommendations regarding diet and exercise.[7] The AGP report helps providers identify glucose patterns and provides a breakdown of time in range (TIR), or the time glucose remains between 70 mg/dL and 180 mg/dL.[8] Current recommendations from the American Diabetes Association indicate that a goal A1c less than 7% is equivalent to TIR greater than 70% in adults.[8] Repeat evaluation of TIR at subsequent patient visits can be utilized as a discussion point for evaluation of progress.[7]

Despite helpful utility of these devices for providers and patients, historically CGM use has remained low due to cost prohibiting patient access and lack of provider awareness about devices available, ordering processes, and data utilization.[7] Many insurance companies, both commercial and government entities, have criteria for approval of CGM devices – with significant barriers being documentation of multiple daily injection use, checking blood glucose 3-4 times daily, and making adjustments to their insulin regimen based on these results. In addition, for patients with Medicare and Medicaid, physicians may be required to order the CGM device through a durable medical equipment (DME) provider – adding further complexity and time to the process of acquisition. If CGMs are not covered by insurance, patients may pay cash for these devices. Cost may range between approximately $130 to $450 for a 30 day supply dependent on type of CGM requested.[9,10]

Clinical Conundrums

As of April 16, 2023, the Centers for Medicare and Medicaid Services (CMS) has revised CGM coverage criteria to expand the use of CGM – a huge win for patient access.[11] New criteria guidelines for CGM use are summarized below:

- For patients currently using insulin therapy – no longer needing documentation of number of times a patient is checking their blood glucose or making frequent adjustment based on blood glucose readings.[11]
- For patients with history of problematic hypoglycemia – defined as more than one hypoglycemic event (<54mg/dL) that persists regardless of medication changes OR one hypoglycemic event characterized by altered mental state requiring assistance for treatment.[11]

This update will allow Medicare beneficiaries both with and without insulin-dependent diabetes to have easier access to this critical technology. The elimination of frequent insulin adjustment criteria will allow for expanded access to all insulin utilizers, lessening the burden of disease for those on this high-risk medication. In addition to these new criteria, there are notable coverage specifications to ensure appropriate use (**Table 1**).[11] Provider criteria for prescribing CGMs has also been defined to include patient education on proper use of the selected device as well as routine clinic visits (via in-person or telehealth) every 6 months to evaluate progress of diabetes management and continued use of CGM.[11]

The expanded coverage of CGMs is significant for patients on government-funded insurance, such as Medicare or Medicaid. As of May 2023, commercial health insurance requirements for CGMs are largely dependent on benefit packages associated with the plan selected by the patient – but overall varies widely on coverage of CGM devices. Commercially insured patients should be directed that have questions pertaining to CGM use to contact their specific health plan to determine coverage and copay options.

Table 1 | Centers for Medicare and Medicaid Services Criteria for CGM Use[11]

Type of CGM Coverage	Qualifications for Use
Initial (New Prescription for Use)	Diagnosis of diabetes ***AND*** Sufficient training of CGM has been provided ***AND*** On insulin therapy ***OR*** history of documented problematic hypoglycemia classified as: • 2 or more blood glucose <54 mg/dl requiring medication adjustment • Blood glucose <54 mg/dl characterized by altered mental/physical state
Continued (Renewal for Use)	Billable visit (in-person or via telehealth) every 6 months with documentation of adherence to CGM and diabetes treatment plan

Clinical Conundrums

Ultimately, expanded access of CGM use for Medicaid and Medicare beneficiaries reduces the implicit biases at the prescriber level, and opens access regardless of medication use and insurance status.[7] Progress to promote patient-centered care is important for every patient and provider – and continued expanded access for CGMs should be promoted.

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Over-the-Counter

For Use Only in Cinnamon Rolls? Evaluating OTC Cinnamon for Blood Glucose Control

Christie Monahan, PharmD

Providers are commonly asked about natural medicine remedies on the market, particularly those with advertisements promoting the ability to reduce blood glucose. Several supplements on the market, such as garlic, ginger, turmeric, and green tea are among the most commonly used for glucose control, but have limited evidence to support use.[1,2] According to The Botanical Institute, while multiple supplements can help with blood glucose control, cinnamon is recommended before others to stabilize blood sugar and may be requested by patients.[2]

Cinnamon is a spice made from bark of the *Cinnamomum verum* tree native to South America and the West Indies that requires at least 2 years of growth prior to harvesting.[3,4] While the tree produces both flowers and leaves, the bark alone is useful for spice-making and undergoes a drying process prior to human consumption.4 Cinnamon use has been noted as early as 2000 BCE for its medicinal properties, including reducing inflammation,

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lowering cholesterol, and fighting bacterial infections as well as use for flavoring and baking purposes.[5]

While routine and recommended use for cinnamon regarding the reduction of blood glucose is still unclear, some studies have shown promising results. In 2019, Roghayeh et al. performed a triple-blind placebo-controlled randomized clinical trial evaluating the effect of cinnamon supplementation on anthropometric, glycemic and lipid outcomes of patient with type 2 diabetes based on baseline body mass index (BMI).[6] Treatment arms includes those taking cinnamon 500mg capsules twice daily versus parallel placebo for the duration of 3 months. Results found improvement, not significance, in BMI, total body fat, glycemic measures (including glucose, A1c reduction, and insulin resistance), and lipids (including total cholesterol, LDL, and HDL). Statistically significant results noted for individuals with baseline BMI > 27.[6] A similar study evaluated the effect of adding cinnamon dosed at 3000mg daily to patients on an existing oral antidiabetic regimen, with results favoring a reduction in A1c by 0.2% and fasting blood glucose of 2.2mg/dL after 90 days.[7] Other studies have found cinnamon at 1500mg daily or more to have reduction on fasting glucose levels and insulin resistance in patients with prediabetes and diabetes.[8,9] Notably all studies reviewed stated limitations with duration of study length, standardized dosing regimens, and need for continued research for long-term use.[6-9]

Overall, data to support the use of cinnamon is limited, but some studies may have noted potential health benefits. However, the American Diabetes Association does not currently recommend cinnamon to reduce blood glucose levels.[10] While use may provide marginal benefit for glucose control, patients with a known allergy may experience harm as well as those suffering from esophageal reflux disease may tolerate direct ingestion poorly.[2] If patients are inquiring about use of cinnamon for glucose control, extensive discussion involving the potential risks and limited data should be discussed.

In addition, supplements are not regulated by the Food and Drug Administration (FDA), and patients should be advised to select over-the-counter products with USP or NSF labeling to ensure proper laboratory handling, purification, and the allotment of cinnamon product in each dosage form is consistent (**Figure 1**).[11] Current clinical recommendations for blood glucose management include a low carbohydrate diet, regular exercise, and use of prescription medication as prescribed by a healthcare provider.[10] However, if patients continue to want to add cinnamon to their diet, it is advised to sprinkle on food or cook with about one-half teaspoon to one teaspoon daily.[1] Use of cinnamon in its whole form in food, instead of in a tablet or capsule, is suggested due the overall lack of data involving the use of specific cinnamon formulations and standardized quantity advised.[1]

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Figure 1 | United States Pharmacopeia Convention Seals of Approval[11]

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Device Debrief

Freestyle Libre 3® Continuous Glucose Monitor

Christie Monahan, PharmD

Continuous glucose monitors (CGMs) have evolved over the years, and there have been exciting improvements in the accuracy, reliability, and ease of use for these devices. However, there are some specific differences between the two main types of CGMs, real-time and intermittently scanned, to consider when choosing a system (**Table 1**).

Real-time CGMs, broadly speaking, are systems made up of three components: the sensor (a small wire catheter that is inserted under the skin on your arm or abdomen), a transmitter that attaches to the sensor, and a handheld receiver and/or smartphone that displays glucose data in real time.[1] Be advised that each manufacturer may have slightly different components. These systems oftentimes offer alerts for patients, either audibly or via notification, of blood glucose trends due to the continuous transmission of data. In addition, patients can share login ability with caregivers or family members for safety and eliminates the need for fingerstick. Devices can also be paired to healthcare facilities as well with a shared code, allowing providers to access CGM data conveniently during a patient visit. Unfortunately, due to the advanced features of these real-time systems, cost may be a barrier and patients should be informed about potential for higher copays and paperwork for insurance coverage up front.[1]

In contrast, intermittently scanned CGM systems require manual scanning of the device to obtain and store blood glucose data. Historically, these devices use less components: a combined glucose sensor/transmitter however, the Dexcom G7® is a real-time CGM with two components.[1] The types of readers will vary for these devices, either as a separate touchscreen device or utilization of patient's smartphone. These systems tend to be easier to use and more affordable. Similar to real-time CGMs in ability

Device Debrief

to share data with others and prevent use of fingerstick for manual glucose checking. Some cons of this type of system include limitations with calibration and manual intention for scanning (every 8 hours). If a patient forgets to scan their device every 8 hours, data loss will occur, and complete evaluation of continuous blood glucose monitoring is unable to be achieved.[1]

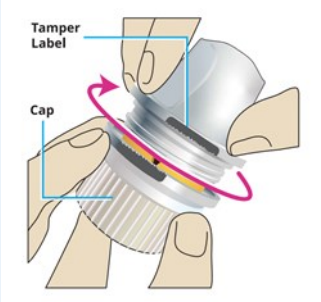
Patients should take the time to investigate both options based on individual lifestyle and support. Providers can assist with this decision by discussing the differences between available options, including updated information regarding cost, and ensuring proper training is conducted. Patients should be encouraged to continue provider follow-up for diabetes management and link CGM data to clinic for ongoing access for provider use to support change in treatment decisions.

The following directions for use pertain to the Freestyle Libre 3®, a real-time CGM from Abbott®. This CGM was recently released in late 2022, with promoted reduced copay costs and a smaller size (two stacked pennies tall) than predecessor. This version is also compatible for smartphone use (via the Freestyle Libre 3® app) and does not offer the use of a separate reader device.[2] Blood glucose readings are continuously transmitted to smartphone device and able to be shared with caregivers, family members, and providers. No manual swiping of device needed, and alerts can be tailored to preference, although glucose control between 70mg/dl and 180mg/dl is recommended for A1c goal <7% and a time in range of >70%.[2]

Patients should be advised prior to inserting the CGM to download the Freestyle Libre 3® app for completion of setup process. The CGM device should be inserted into the back of the upper arms, ensuring the application site is cleaned with soap and water or rubbing alcohol, and to avoid scars, stretch marks, lumps, tattoos, and insulin injection sites. To prevent skin irritations, patients should be encouraged to rotate sites between uses every 14 days.[3]

The Freestyle Libre 3® device itself comes self-contained with the insertion device and sensor (**Figure 1**). Patients should only use the device if the tamper cap is unaltered and should not touch the inside of the sensor prior to application to the skin.[3]

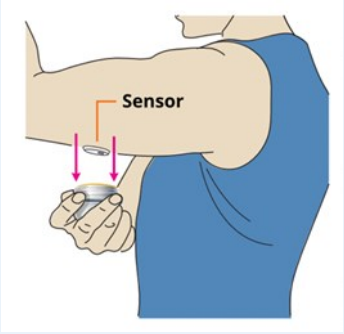
Figure 1



Patients should be advised to wipe area with alcohol and let dry for 10-15 seconds. Providers can write a prescription for alcohol wipes for potential insurance coverage and to ensure they are dispensed by the pharmacy or durable medical equipment company. To place the device on the body, patients will remove the cap and press against the cleaned skin firmly until an audible "click" is heard. Gently remove the sensor applicator away from the body (**Figure 2**).[3]

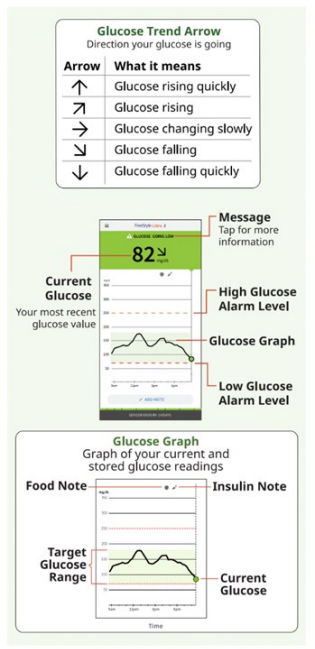
Device Debrief

Figure 2



The device is now inserted into the arm successfully, and the cap and applicator can be thrown away. Patients should ensure the device is well applied to the arm by checking the adhesive around the sensor is flat and firmly stuck to the skin. Completion of the CGM setup happens with the Freestyle Libre 3® app, including the warm-up of the sensor (60 minutes) and setting up of alarms. Patients will be able to trend blood glucose, with anticipatory actions based on historical patterns (**Figure 3**) and providers will be able to request CGM shared data. Device education for the patient should be completed at time of initial setup with alarms enabled to notify of hypoglycemia events warranting treatment.[3]

Figure 3



If patients have any questions or concerns regarding use of the Freestyle Libre 3®, help is available at their local pharmacy and at Abbott® Support (855-632-8658). Additional resources and assistance can also be found online.[3]

References:

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Drug Update:
New Indications and Dosage Forms
June 2023

Veozah® (fezolinetant) Tablet
New Molecular Entity: Indicated for treatment of moderate to severe hot flashes from menopause; works by blocking the NK3 receptor that plays a role within the brain to regulate body temperature

Inpefa® (sotagliflozin) Tablet
New Molecular Entity: Dual mechanism SGLT1 and SGLT2 inhibitor indicated for reducing risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in patients with T2DM and CKD

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Supplementary Appendix

Supplement Table 3 | Summary of Literature for CYP2B6 and Combined CYP2C19 Recommendations[5,10-12]

Reference	Study Design	Phenotype/Genotype	Outcomes
Yuce-Artun et al.[10] (2016)	Prospective observational study investigating impact of *CYP2B6* and *CYP2C19* variants on SERT serum levels and N-DSERT in 50 Turkish patients treated for MDD and stable on SERT for ~1 month	*CYP2B6* NM (*1/*1, IM (*1/*6), PM (*6/*6, *6/*9. No UMs (*4/*4) or RMs (*1/*4) detected. *CYP2C19* RM (*1/*17), NM (*1/*1), IM (*1/*2, *2/*17), PM (*2/*2). No UMs.	• Mean N-DSERT/SERT ratios were significantly lower in CYP2B6 IMs and PMs (27.6% and 49.6%, respectively) vs NMs (p=0.011). • Dose normalized SERT values were 1.3 to 2.2-fold higher in CYP2B6 IMs and PMs vs NMs (p=0.019). • Among CYP2C19 IMs and PMs, N-DSERT/SERT ratio was 51.5% lower in CYP2B6 IM and PMs vs NMs.
Saiz-Rodriguez et al.[12] (2018)	Two bioequivalence cross-over (7-day washout) RCTs of 48 healthy individuals from Spain receiving two formulations of SERT 100mg daily	*CYP2B6 c.516G>T* NM (GG), IM (GT), PM (TT) *CYP2C19* UM (*17/*17), RM (*1/*17)[a], NM (*1/*1)[b], IM (*1/*2, *1/*3, *2/*17[a]). No PMs detected.	• Polymorphisms in *CYP2C19* and *CYP2B6* influenced SERT PK, with a greater effect of *CYP2C19*. No significant effect was found for *CYP2C9, CYP2D6* and *ABCB1* polymorphisms. • CYP2C19 IMs and CYP2B6 PMs had higher AUC and longer half-live vs NMs, although AUC (p=0.069) was not significant for CYP2B6. • Observed an association of increased adverse drug reactions in individuals with higher AUC CYP2C19 IM and CYP2B6 PM).
Parikh et al.[11] (2022)	Meta-analysis of 3 studies: GUIDED trial (RCT), Yuce-Artun et al, and Saiz-Rodriguez et al. Examined clinical validity of combined and single-gene PGx algorithm to predict SERT serum levels of 147 patients on SERT therapy for MDD.	*CYP2B6* UM (*4/*4), RM (*1/*4), NM (*1/*1), IM (*1/*6, *4/*6, *1/*9, *4/*9), PM (*6/*6, *9/*9). *CYP2C19* UM (*17/*17), RM (*1/*17), NM (*1/*1), IM (*1/*2, *1/*3, *2/*17), PM (*2/*2, *3/*3, *2/*3)	• Mean sertraline plasma concentrations in CYP2Bg PMs were 52% higher than CYP2B6 NMs (95% CI [0.21,0.84]) in the combined analysis • Mean AUC was 42% lower in CYP2C19 Ums (p=0.03) and 179% higher in PMs (p=0.0005) vs NMs. No significant AUC differences between CYP2C19 RMs (p=0.8) or IMs (p=0.16) vs NMs. • Combinatorial PGx algorithm (CYP2C19 and CYP2B6) identified 36% more patients with significantly decreased SERT metabolism, than CYP2C19 alone; consequently, those 36% were not identified or considered for changes in SERT therapy.
Braten et al.[5] (2022)	Study investigated impact of *CYP2C19* and *CYP2B6* variants on SERT serum levels, with the emphasis on the novel CYP2C:TG haplotype, in 840 Norwegian psychiatric patients.	*CYP2B6* UM (*4/*4), RM (*1/*4)[a], NM (*1/*1), IM (*1/*6, *4/*6, *1/*9, *4/*9), PM (*6/*6, *9/*9). *CYP2C19 + CYP2C:TG* UM (*17/*17, *17/CYP2C:TG, CYP2C:TG/TG), RM (*1/*17, *1/CYP2C:TG), NM (*1/*1), IM (*1/*2, *1/*3), PM (*2/*2, *3/*3, *2/*3)	• CYP2B6 IMs and PMs had a 15% (p<0.001) and 25% (p=0.008) increased SERT serum concentration, respectively, vs NMs • CYP2B6 UMs and RMs had a 17.4% (p=0.022) decreased SERT serum concentration vs NMs. • CYP2B6 Ums/RMs + CYP2C19 Ums (including CYP2C:TG haplotype) had 35.4% lower predicted SERT serum concentrations vs CYP2B6 + CYP2C19 NMs. • CYP2C19 + CYP2B6 PMs had a 2.9-fold increased predicted SERT serum concentration vs CYP2B6+CYP2C19 NMs.

Phenotypes above follow updated CPIC classification, phenotypes reports differ as follows: [a]referred to as ultrarapid metabolizer (UM), [b]referred to as extensive metabolizer (EM); sertraline (SERT), N-desmethylsertraline(N-DSERT), Genomics Used to Improve DEpression Decisions (GUIDED) trial, randomized control trial (RCT)