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Pombiliti™ with Opfolda™ for Late-Onset Pompe Disease

By: Jenna Len, Pharm.D., MBA

What is Pompe Disease? Pompe disease (PD), also known as glycogen storage disorder type II, is an inherited autosomal recessive neuromuscular condition characterized by acid alpha-glucosidase (GAA) enzyme deficiency.[1] The GAA deficiency results in the intralysosomal accumulation of glycogen causing debilitating muscle weakness throughout the body.[2] Common symptoms of PD include fatigue, myalgia, and exercise intolerance which can progress to respiratory insufficiency. This disease is classified as infantile-onset Pompe disease (IOPD) or late-onset Pompe disease (LOPD).[1] Patients with LOPD have delayed disease presentation compared to IOPD, with IOPD presenting within the first 12 months of life and LOPD presenting from 1 year into adulthood.[3]

What agents are currently available to treat Pompe Disease? The available agents approved by the Food and Drug Administration (FDA) for PD include alglucosidase alfa (Lumizyme®; Sanofi Genzyme), avalglucosidase alfa-ngpt (Nexviazyme®; Sanofi Genzyme), and the combination therapy of cipaglucoside alfa-atga (Pombiliti™; Amicus Therapeutics) with miglustat (Opfolda™; Amicus Therapeutics).[4-7] Lumizyme® received FDA approval in May 2010 for both IOPD and LOPD. Nexviazyme® was approved in August 2021 for patients ≥ 1 year of age with LOPD. Pombiliti™ and Opfolda™ were approved in September 2023 for LOPD in adult patients ≥40 kg not adequately responding to their current enzyme replacement therapy (ERT).[4,5]

What is the mechanism action of Pombiliti™ with Opfolda™ compared to Lumizyme® or Nexviazyme®? Pombiliti™ is a synthetic enzyme that serves as an exogenous source of GAA.[4] Opfolda™ is an enzyme

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Mirikizumab for Moderate-to-Severe Ulcerative Colitis

By: Lauren Osadczuk, Pharm.D.

Background: Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) that primarily affects the colon and rectum.[1] There are about 3 million people with IBD in the United States, with UC accounting for half of those cases and Crohn's disease (CD), the other half.[2] Most patients are diagnosed with UC between 15 and 30 years of age.[1,3] Common symptoms of this disease state are abdominal pain, diarrhea, rectal bleeding, and bowel movement urgency.[4] The recommended treatments for long-term management of moderate-to-severe UC include anti-tumor necrosis factors (infliximab, adalimumab, golimumab), an interleukin 12/23 antagonist (ustekinumab), an integrin antagonist (vedolizumab) and a Janus kinase inhibitor (tofacitinib).[4,5] Increased risk of infection or cancer as well as a loss of clinical efficacy over time limit the use of these agents.[6] Mirikizumab–mrkz (Omvoh™; Lilly and Company), another

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stabilizer that delays degradation of Pombiliti™. While the mechanism of action of Pombiliti™ is similar to Lumizyme® and Nexviazyme® (both are exogenous sources of GAA), the addition of an enzyme stabilizer allows for delayed metabolism of Pombiliti™ enabling a greater concentration of GAA to reach the site of action.

What clinical trial led to the FDA approval of the combination of Pombiliti™ with Opfolda™? Pombiliti™ with Opfolda™ was evaluated in the Phase 3 PROPEL trial, a double-bind, multinational, randomized controlled trial that compared the two-component regimen to alglucosidase alfa and placebo in LOPD.[8] Eligible patients were ≥18 years of age, diagnosed with LOPD, and weighed ≥40 kg. Patients (N=125) were randomized in a 2:1 ratio, stratified by 6-minute walk distance (6-MWD) and previous enzyme replacement status, (ERT-experienced vs ERT-naïve), to receive oral Opfolda™ (195 mg for patients ≥40 kg to <50 kg, 260 mg for patients ≥50 kg) given 1 hour before intravenous (IV) Pombiliti™ (n=85) or oral placebo and IV alglucosidase alfa (n=40). Both ERTs were dosed at 20 mg/kg IV every 2 weeks. The primary outcome was the baseline to 52-week change in 6-MWD. A comparative safety analysis was also conducted. In the intention-to-treat group, the mean change in 6-MWD from baseline to week 52 was 20.8 meters (m) in the Pombiliti™ with Opfolda™ group vs 7.2 m in alglucosidase alfa and placebo group [between-group-distance: 13.6 m (95% CI -2.8 to 29.9)]; this result was not statistically significant. However, ERT-experienced patients in the Pombiliti™ with Opfolda™ group (n=65) demonstrated an overall improvement in the 6-MWD from baseline to week 52, with a period of stabilization between week 12 and week 38, while the ERT-experienced patients in the algulcosidase alfa plus placebo group (n=30) showed an initial small improvement at week 12 in the 6-MWD followed by stabilization through week 38 and a return to baseline values by week 52 (between-group difference: 16.9 m; P=0.047). Pombiliti™ with Opfolda™ group demonstrated a clinically meaningful improvement in motor function when compared to standard of care for ERT-experienced patients. The occurrence of adverse events was similar between the Pombiliti™ with Opfolda™ group versus the alglucosidase alfa and placebo group (96% vs 97%, respectively).

What are some safety concerns with Pombiliti™ and Opfolda™? Pombiliti™ has three black box warnings: 1) Hypersensitivity reactions including anaphylaxis, 2) Infusion-associated reactions, and 3) Risk of acute cardiorespiratory failure in susceptible patients.[4] Common side effects of both Pombiliti™ and Opfolda™ with an incidence of >5% include headache, diarrhea, fatigue, nausea, abdominal pain, and pyrexia.[4,5] Pombiliti™ and Opfolda™ are contraindicated in pregnancy; pregnancy status should be verified in females of reproductive potential prior to initiation of therapy.

What is the recommended dose and administration of Pombiliti™ with Opfolda™? The recommended dose of Pombiliti™ is 20 mg/kg (based on actual body weight) via IV infusion over ≥4 hours every other week.[4] The Pombiliti™ infusion can be gradually increased by 2 mg/kg/hour every 30 minutes, if there are no signs of hypersensitivity or infusion-associated reactions, to a maximum rate of 7 mg/kg/hour which may be maintained until completion. Opfolda™ is given as an oral dose of 195 mg for patients ≥40 kg to <50 kg and 260 mg for patients ≥50 kg every other week.[5] Opfolda™ should be taken with an unsweetened beverage about 1 hour prior to the Pombiliti™ infusion, no other beverages or food should be consumed 2 hours before and after taking Opfolda™. The IV infusion of Pombiliti™ should be started 1 to 3 hours after oral administration of Opfolda™. If the Pombiliti™ infusion is delayed beyond 3 hours, the combination should be restarted ≥24 hours after the dose of Opfolda™ was taken. If the Opfolda™ dose is missed, Pombiliti™ should NOT be administered and the combination should be rescheduled.

What is the cost and availability of Pombiliti™ with Opfolda™? Pombiliti™ for injection 105 mg vial (NDC 71904-200-01) has an average wholesale price (AWP) of $2,142.[9] Opfolda™ 65 mg capsule (NDC 71904-300-01) has an AWP of $39.[10] The estimated annual cost for an 80 kg patient to receive combination therapy with these medications would be approximately $800,000.

What is the formulary status of Pombiliti™ with Opfolda™? Pombiliti™ and Opfolda™ were added to the Adult CCHS Formulary restricted to the Department of Hematology/Oncology for outpatient use only.

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potential therapeutic option for UC, received approval by the Food and Drug Administration (FDA) in October 2023 for moderate-to-severe UC in adults.[7]

Mechanism of Action: Mirikizumab inhibits the interaction between interleukin-23 (IL-23) and the IL-23 receptor by binding to the p19 subunit of IL-23, thus inhibiting the release of pro-inflammatory cytokines and chemokines.[7] Of note, risankizumab-rzaa (Skyrizi®; Abbvie) is another biologic agent with the same mechanism of action as mirikizumab, but is currently only FDA-approved for moderate-to-severe Crohn's disease.[8]

Clinical Trials: LUCENT-1 and LUCENT-2 were randomized, double-blind, parallel-group, and placebo-controlled trials that evaluated the efficacy and safety of mirikizumab induction and maintenance therapy in patients with moderate-to-severe UC.[6] Eligible patients were 18 to 80 years of age with moderate-to-severe UC and previous treatment failure, loss of response, or intolerance to one or more therapies for UC. Moderate-to-severe UC was defined as a modified Mayo score from 4 to 9 with an endoscopic subscore of 2 or 3. Mayo scores are commonly used to assess UC severity and consist of four subcategories, each scored between 0 and 3. These subcategories are stool frequency, rectal bleeding, endoscopic findings, and physician assessment. The modified Mayo score removes physician assessment, resulting in an overall possible score between 0 and 9. In LUCENT-1, patients (N=1162) were randomized 3:1 to receive induction therapy with intravenous (IV) mirikizumab 300 mg (n=868) or placebo (n=294) at weeks 0, 4, and 8. Patients (N=544) with a clinical response to mirikizumab at week 12 were randomized 2:1 to maintenance therapy with subcutaneous mirikizumab 200 mg (n=365) or placebo (n=179) every 4 weeks for 40 weeks in LUCENT-2. Clinical response in LUCENT-1 was defined as a decrease of at least 2 points in the modified Mayo score with a decrease of at least 30% from baseline, plus a rectal sub-score of 0 or 1 or a decrease in rectal sub-score of at least 1 point from baseline. The primary endpoint for LUCENT-1 and LUCENT-2 was clinical remission at weeks 12 and 40, respectively. Clinical remission for both trials was defined as a modified Mayo stool frequency sub-score of 0 or a stool frequency sub-score of 1 with a decrease of at least 1 point from baseline, a rectal bleeding sub-score of 0, and an endoscopic sub-score of 0 or 1 (excluding friability). By week 12 of LUCENT-1, 24.2% of patients in the mirikizumab group and 13.3% of patients in the placebo group achieved clinical remission (11.1 percentage points difference; 99.875% confidence interval (CI), 3.2 to 19.1; P<0.001). By week 40 of LUCENT-2, 49.9% of patients in the mirikizumab group and 25.1% of patients in the placebo group had achieved clinical remission (23.2 percentage points difference, 95% CI, 15.2 to 31.2; P<0.001). The authors of LUCENT-1 and LUCENT-2 concluded that mirikizumab was safe and effective for induction and maintenance therapy in patients with moderate-to-severe UC.

Safety: Common adverse reactions associated with IV mirikizumab include respiratory tract infection (8%) and arthralgia (2%).[7] The most frequent adverse reactions with subcutaneous mirikizumab include upper respiratory tract infection (14%), arthralgia (7%), injection site reaction (9%), rash (4%), headache (4%), and herpes viral infection (2%).[6] Prior to initiation of mirikizumab, patients should be evaluated for tuberculosis infection. Due to one reported case of mirikizumab-induced hepatotoxicity during a longer than usual induction period, it is recommended that liver enzyme and bilirubin levels be assessed at baseline and for at least 24 weeks of treatment. Other therapies should be considered in patients with liver cirrhosis. Live vaccines should be avoided during mirikizumab therapy due to the risk of infection.

Dosing and Administration: Mirikizumab is administered as a 300 mg IV infusion at weeks 0, 4, and 8 for induction.[7] Mirikizumab solution must be diluted with 50 to 250 mL of 0.9% sodium chloride or 5% dextrose and administered over at least 30 minutes through a dedicated line. Maintenance dosing for mirikizumab is 200 mg given subcutaneously every 4 weeks. Of note, each 200 mg dose is administered as two consecutive injections using the 100 mg prefilled pens. Patients may self-administer subcutaneous mirikizumab in the abdomen, thigh, or back of the upper arm.

Cost and Availability: Mirikizumab is available as a 300 mg/15 mL single-dose vial (NDC 0002-7575-01).[7] The average wholesale price per vial is $11,512.[9] Mirikizumab is also available as a 100 mg/mL pre-filled pen (NDC 0002-8011-27).[7] Two 100 mg pens are included in each package with an average wholesale price per package of $12,433.[9] The estimated annual cost of mirikizumab including induction and monthly maintenance therapy is approximately $160,000.

Formulary Status: Intravenous mirikizumab is on the CCHS Adult Formulary restricted to the Department of Gastroenterology for outpatient use only.

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