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5/21/2024

Pharmacy and Therapeutics Committee
Oregon State University
500 Summer Street NE, E35
Salem, Oregon 97301-1079

RE: June 6th P&T Committee Hearing - Drugs for Weight Loss Prior Authorization Update

The Obesity Action Coalition (OAC) appreciates the opportunity to comment on the Oregon State University Pharmacy and Therapeutics Committee hearing regarding the use of semaglutide (WEGOVY) in patients with cardiovascular (CV) disease who are affected by obesity. The OAC is a national non-profit organization dedicated to giving a voice to individuals affected by the disease of obesity.

We are pleased that the Oregon P&T committee will be considering prior authorization (PA) criteria to allow coverage of semaglutide (WEGOVY) for secondary prevention of major CV events. We commend the state for quickly moving to update existing coverage policies to align with advances in science and clinical standards. The revised prior authorization criteria should promote access to semaglutide consistent with the new indication for the use of Wegovy to reduce the risk of heart attack and stroke in those living with obesity who also have a history of heart disease.

The OAC proudly serves about 1,000 members living in Oregon and is backed by more than 85,000 members across the United States. We applaud this new indication, as it improves access to obesity care and updates state policies into alignment with advances in science and clinical standards. Throughout the past decades, the prevalence of obesity has skyrocketed across our country and in Oregon – with 31 percent of adults and more than 14.5 percent of children (ages 10-17) in the state currently affected by obesity. Approximately 42% of American adults are affected by obesity, a chronic disease that increases the risk for premature death and a variety of health problems, including heart attack and stroke.

Obesity is driven by strong biology, not by choice and is often the root cause and driver of other health complications. A 2023 report found that treating obesity can reduce diabetes (-8.9%), hypertension (2.3%), heart disease (-2.6%), cancer (-1.3%), and disability (-4.7%) over 10 years in private insurance coverage and Medicare. The same assumptions can also be applied to Medicaid and state employee health plans. (Benefits of Medicare Coverage for Weight Loss Drugs. By Alison Sexton Ward, PhD, Bryan Tysinger, PhD, PhuongGiang Nguyen, Dana Goldman, PhD and Darius Lakdawalla, PhD. USC Schaeffer, 2023.)

Obesity is a complex chronic disease that extends beyond individual lifestyle choices to encompass a broader landscape of social determinants and systemic factors, contributing significantly to health inequities. Disparities in obesity rates are often closely intertwined with socioeconomic status, geographic location, and access to resources. Individuals in marginalized communities may face barriers to affordable and nutritious food options, safe spaces for physical activity, and unequal access to qualified providers of quality healthcare. These structural inequities exacerbate the prevalence of obesity among vulnerable populations, leading to a cycle of poor health outcomes. Tackling obesity requires a comprehensive approach.

There are multiple evidence-based treatments for people with obesity that mitigate the impacts of the disease and improve health outcomes. Unfortunately, the present landscape of obesity treatment coverage remains piecemeal and laden with arbitrary hurdles to receive comprehensive care. For example, while Oregon Medicaid does provide coverage for nutritional counseling and intensive behavioral therapy as well as coverage for metabolic and bariatric surgery (with limitations), the plan does not offer coverage for FDA-approved obesity medications.

We respectfully request that in the near future, the P&T committee consider adding coverage of obesity medications which would reduce other Medicaid costs associated with the disease and ensure that state policies do not discriminate against individuals with obesity as compared to other highly prevalent health conditions.

Our country must acknowledge obesity for the chronic disease that it is and take steps to treat it in the same serious fashion as other chronic disease states such as diabetes and hypertension. We encourage the Oregon P&T committee to approve the prior authorization (PA) criteria to allow coverage of semaglutide (WEGOVY) for secondary prevention of major CV events. As a voice for people living with obesity, OAC looks forward to working with the state of Oregon to ensure all Medicaid recipients have access to comprehensive obesity care for this complex and chronic disease.

We would be happy to meet and share further information and perspectives of people living with obesity. Should you have questions or need additional information, please reach out to our Policy Advisor, Chris Gallagher at chris@potomaccurrents.com. Thank you.

Sincerely,

Joseph Nadglowski, Jr.
OAC President and CEO

Auvelity® (dextromethorphan HBr and bupropion HCl) Handout for Oregon P&T Meeting June 6th, 2024

Epidemiology and Unmet Need	• MDD is a potentially life-threatening condition and is also the leading cause of disability worldwide.[1,2] • More than two-thirds of individuals with MDD have severe functional impairment.[3] • Despite numerous treatment options for MDD, many challenges exist including delayed therapeutic effect, low rates of remission, and intolerable side effects.[4] • Early clinical improvement with antidepressant therapy has emerged as an important treatment consideration, as it has been associated with significantly improved prognosis, remission, and long-term outcomes.[5,6] • Prior to approval of Auvelity, traditional oral MDD therapies have shared similar mechanisms of monoaminergic modulation.[7] • Importantly, after ineffective SSRI treatment, the likelihood of remission with switching to another monoamine-based treatment, whether another SSRI, an SNRI, or bupropion, is only ~20% based on the STAR*D study.[8] • The lack of pharmacologic diversity among oral treatments has been a well-recognized area of unmet need and a focus of drug development for over 20 years.
Mechanism of Action	• Auvelity is the first and only oral N-methyl D-aspartate (NMDA) receptor antagonist approved for the treatment of MDD and represents the first oral treatment whose mechanism is not primarily monoaminergic. • Dextromethorphan is an antagonist of the NMDA receptor and a sigma-1 receptor agonist.[9] NMDA receptor antagonism and sigma-1 receptor agonism modulate glutamatergic neurotransmission. • The role of bupropion in AUVELITY is primarily to increase and prolong plasma levels of dextromethorphan, by inhibiting its CYP2D6-mediated metabolism. Bupropion is also a relatively weak inhibitor of the dopamine and norepinephrine transporters.[9]

Clinical Development of Auvelity	• Breakthrough therapy designation was granted to Auvelity in 2019 by the FDA and it was approved in August 2022 based on a clinical development program of over 1100 patients.
	• In the pivotal, placebo-controlled, Phase 3, **GEMINI study:**
	  ○ Auvelity achieved the primary outcome: Change from baseline to week 6 in MADRS total score was -15.9 points in the Auvelity group and -12.1 in the placebo group (*P*=0.002).[9,10]
	  ○ Statistically significant improvement in the MADRS was demonstrated starting at Week 1,[9,10] a time frame consistent with the draft FDA guidance for rapid-acting antidepressants.[11]
	  ▪ No other oral antidepressant has FDA-approved labeling stating improvement in depressive symptoms starting at Week 1.
	  ○ The improvements seen with Auvelity were greater than the minimum clinically important threshold on the MADRS, which ranges from 1.6-1.9 points, at all timepoints measured.[10,12]
	  ○ The key secondary endpoint of remission (MADRS Total Score ≤10) at Week 2 was also achieved, with Auvelity demonstrating a statistically significant greater remission rate compared to placebo (Auvelity 17%, Placebo 8%; *P* = 0.013).[10]
	  ▪ Symptom remission is considered the desired goal in depression treatment, because it is associated with better daily functioning and better long-term prognosis.[13]

	• In the confirmatory, active-controlled, Phase 2, **ASCEND study:**
	  ○ Auvelity achieved the primary outcome by demonstrating statistically significant improvement in change from baseline in MADRS total score over weeks 1-6 compared to bupropion 105 mg dosed twice daily (Auvelity -13.7 points, Bupropion -8.8 points; *P* < 0.001).[14]
	  ○ Rates of remission were also increased compared to bupropion starting at Week 2.[14]

Adverse Events and Other Important Safety Information	• Auvelity has a boxed warning for increased risk of suicidal thoughts and behaviors in pediatric and young adult patients.[9] • The most common (incidence ≥5% for Auvelity and more than twice as frequently as placebo) adverse reactions with Auvelity were dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.[9] • Please consult the Auvelity full Prescribing Information (https://www.axsome.com/auvelity-prescribing-information.pdf) for complete product details including contraindications, warnings and precautions, drug interactions, and adverse reactions.
Treatment Guideline	• Auvelity is now among the recommended first line treatments in the recently updated Florida Best Practice Psychotherapeutic Medication Guidelines for Adults with MDD.[15]
Formulation and Other Considerations	• Auvelity is a patented, proprietary, extended-release formulation. • There is no other formulation or combination of dextromethorphan that is approved for the treatment of MDD and there are no generic or therapeutic equivalents for Auvelity. • The doses and release profile of the individual components of Auvelity were determined based on extensive pharmacokinetic studies and result in dextromethorphan concentrations that target the Ki (inhibitory constant) values for the relevant neurotransmitter systems. • Given the non-linear pharmacokinetics of Auvelity,[9] alterations in the dose or recommendations that patients attempt to take the components separately are not advisable and have not been proven to be safe or effective.
Summary	• Auvelity is a novel, oral, rapid-acting antidepressant that addresses important unmet clinical needs in MDD and we ask that it be considered for preferred status on the PDL.

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VEOZAH™ (fezolinetant) tablets, for oral use[1]
One 45 mg tablet orally once daily with or without food [1]
Medicaid Formulary Preferred Drug Listing (PDL) Testimony
Oregon, Thursday, June 6th 2024

Vasomotor Symptoms (VMS) due to Menopause Overview

•The burden of VMS characterized by hot flashes in women undergoing menopausal transition is substantial.[2] VMS can persist for a median of 7.4 years and can have a substantial negative impact on quality of life, contributing to physical and psychosocial impairment that can affect work performance, social activities, and relationships.[2]

Indications and Usage

•VEOZAH is a neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.[1]

Mechanism of Action

•VEOZAH is a neurokinin 3 (NK3) receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/ neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center.[1] The thermoregulatory center in the brain hypothalamus is innervated by KNDy neurons.[3]

Clinical Studies

•Two phase 3 studies were conducted to evaluate the **efficacy** and **safety** of fezolinetant in individuals experiencing moderate to severe VMS associated with menopause. [2,3] The 1,022 women in these studies had a minimum average of 7 moderate to severe vasomotor symptoms per day.[1]

•An additional phase 3 study of 1,830 women was conducted to evaluate the **safety, tolerability**, and effect of fezolinetant on **endometrial health** over 52 weeks in postmenopausal women seeking treatment for VMS associated with menopause.[4]

•The mean age of the postmenopausal women studied was 54 years.[1] Women self-identified as Caucasian (81%), African American (17%), Asian (1%), and Hispanic/Latina ethnicity (24%).[1]

Efficacy

•Data from each trial demonstrated statistically significant and clinically meaningful reductions from baseline in the **frequency** of moderate to severe VMS for VEOZAH 45 mg compared to placebo at Weeks 4 and 12.[1]

- Clinically meaningful was defined by the FDA as a reduction of ≥2 hot flashes over 24 hours vs placebo. [1]

•Data from each trial also demonstrated a statistically significant reduction from baseline in the **severity** of moderate to severe VMS (over 24 hours) at Weeks 4 and 12 for VEOZAH 45 mg compared to placebo. [1]

Safety

•In the VEOZAH 45 mg dose group across the 3 trials, endometrial biopsy assessments identified one case of endometrial hyperplasia and one case of endometrial malignancy. The rate of these events in the VEOZAH 45 mg dose group was ≤ 1%.[1]

Contraindications

VEOZAH is contraindicated in women with any of the following conditions:

•Known cirrhosis •Severe renal impairment or end-stage renal disease •Concomitant use with CYP1A2 inhibitors[1]

Warnings and Precautions

•Hepatic transaminase elevation: Elevations in serum transaminase concentrations greater than three times the upper limit of normal (ULN) occurred in 2.3% of women receiving VEOZAH and 0.9% of women receiving placebo in three clinical trials. No serum elevations in total bilirubin (greater than two times ULN) occurred. Perform baseline bloodwork prior to initiation of VEOZAH to evaluate for hepatic function and injury. Do not start therapy if serum transaminase concentration is equal to or exceeds two times the ULN. Perform follow-up evaluations of hepatic transaminase concentration at 3 months, 6 months, and 9 months after initiation of therapy. [1]

Adverse Reactions

•The most common adverse reactions with VEOZAH [at least 2% in VEOZAH 45 mg and greater than placebo] are: abdominal pain, diarrhea, insomnia, back pain, hot flush, and hepatic transaminase elevation. [1]

This concludes our clinical overview of VEOZAH.

Please click here for full Prescribing Information for VEOZAH (fezolinetant).

References: 1. VEOZAH [package insert]. Northbrook, IL: Astellas Pharma US, Inc. 2. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *The Lancet*. 2023. https://dx.doi.org/10.1016/S0140-6736(23)00085-5. 3. Johnson KA, Martin N, Nappi RE, et al. Efficacy and Safety of Fezolinetant in Moderate-to-Severe Vasomotor Symptoms Associated With Menopause: A Phase 3 RCT. *J Clin Endocrinol Metab.* 2023;(0021-972X (ISSNLinking)). Available at: https://dx.doi.org/10.1210/clinem/dgad058. 4. Neal-Perry G, Cano A, Lederman S, et al. Safety of Fezolinetant for Vasomotor Symptoms Associated with Menopause: A Randomized Controlled Trial. *Obstetrics Gynecol*. 2023; 141(4):737-47. https://dx.doi.org/10.1097/aog.0000000000005114

SPRAVATO® (esketamine)
Oregon Pharmacy and Therapeutics (P&T) Committee Meeting - May 2024

Submitted by Janssen Scientific Affairs, LLC on behalf of Nirmal Ghuman, Principal Scientific Account Lead, Value & Evidence Scientific Engagement – Field

PRODUCT DESCRIPTION

SPRAVATO is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant (AD), for the treatment of:

- Treatment-resistant depression (TRD) in adults.[1]
- Depressive symptoms in adults with MDD with acute suicidal ideation or behavior (MDSI).[1]

Please note Limitations of Use Including:[1]

- The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO.
- SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

SPRAVATO has a boxed warning for sedation, dissociation, respiratory depression, abuse and misuse, and suicidal thoughts and behaviors.
SPRAVATO is a Schedule III (CIII) controlled substance under the Controlled Substances Act. Due to the risks of serious adverse outcomes from sedation, dissociation, respiratory depression, abuse and misuse, SPRAVATO is available only through a restricted program called SPRAVATO Risk Evaluation and Mitigation Strategies (REMS). Further information is available at SPRAVATOrems.com.

New Pertinent Information

SPRAVATO is indicated in adults with TRD and MDSI. We note that the recommended PA criteria does not allow for the use of SPRAVATO in those age 65 or older.

Retrospective Study: REAL-ESK Post Hoc Analysis

d'Andrea et al (2023)[2] evaluated the effectiveness and tolerability of SPRAVATO nasal spray in 30 patients (aged ≥65 years) with TRD in a post hoc analysis of the real-world, retrospective, observational, multicenter REAL-ESK study in Italy. Patients (mean age, 68 years; female, 70%) received SPRAVATO at an initial dose of 28 mg biweekly for 1 month, followed by a once-weekly flexible dosage (28, 56, or 84 mg) based on efficacy for the next 2 months. Most patients were treated with 28 mg (36.7%) or 56 mg (43.3%) doses of SPRAVATO. A response (defined as a 50% overall decrease from baseline in the MADRS) was reported in 8/30 (26.7%) and 16/30 (53.3%) patients at the end of 1 (T1) and 3 (T2) months of treatment, respectively. Additionally, a significant increase in the remission rate was observed at T2 vs T1 (33.3% vs 10%; *P*=0.028). TEAEs occurred in 19/30 (63.3%) patients, including dizziness (50%), dissociation (33.3%), sedation (30%), and hypertension (13.3%). The reported TEAEs were temporary and resolved by the following day at the latest. Treatment discontinuation was reported in 6/30 (20%) patients; 2/30 (6.7%) discontinued treatment due to TEAEs.

Conclusion

In summary,

- The USPI for SPRAVATO does not prevent use in elderly patients 65 years of age and older.[1]
- SPRAVATO has been studied for efficacy and safety in both real world and clinical studies for efficacy and safety in elderly patients 65 years of age and older.

Please consider updating the PA criteria for SPRAVATO to allow coverage for patients older than 65 years of age to ensure providers can treat patients with SPRAVATO per the USPI. Please refer to the full USPI for complete information.

REFERENCES

1. SPRAVATO (esketamine nasal spray) [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf.

2. d'Andrea G, Chiappini S, Mcintyre RS, et al. Investigating the effectiveness and tolerability of intranasal esketamine among older adults with treatment-resistant depression (TRD): a post-hoc analysis from the REAL-ESK study group. *Am J Geriat Psychiatry*. 2023;31(12):1032-1041.

May 29, 2024

Oregon Medicaid P & T Committee

Re: Public Testimony for Teleconference on Prior Authorization Criteria Update: Semaglutide (June 6, 2024)

Dear Committee Members,

I am providing written testimony regarding the Prior Authorization Criteria Update: Semaglutide (published 2024). I am a practicing physician in the Portland area with current ABIM board certification in Internal Medicine and Endocrinology as well as Obesity Medicine. I am currently director of a preventive cardiology center and conduct NIH research into the physiology of weight regulation and the consequences of developing overweight and obesity. As part of my clinical practice, I have been prescribing drugs for weight management for 25 years, focusing specifically on reducing cardiovascular risk in my patients with overweight and obesity during the past 11 years.

First, thank you for addressing this important need. The specific indication under consideration at this meeting for semaglutide 2.4 mg (Wegovy) has both historic and clinical significance. With the publication of the SELECT cardiovascular outcomes trial in 2023,[1] semaglutide 2.4 mg is the first drug within this class proven to reduce major adverse cardiovascular events in patients with overweight and obesity. SELECT was not formally designed as a weight loss trial, but rather a cardiovascular outcomes study. The distinction is important because no predetermined weight loss goal (or any weight loss for that matter) was required and semaglutide dosing could be titrated to tolerability, leaving open the possibility that on-trial dosing could be less than 2.4 mg weekly or take longer than 4 months to achieve. Most significantly, I believe, was that SELECT showed not only a significant 20% reduction in cardiovascular events, but a similar magnitude reduction in risk for death from any cause (Hazard Ratio of 0.81 with 95% CI, 0.71–0.93). Although not formally adjusted in this analysis, both the direction and magnitude of this impact attests to semaglutide's important role not only to prevent heart attacks but also highlights its potential to save lives.

To give perspective on its secondary cardiovascular benefits, it is important to point out that participants in the SELECT trial at the time of enrollment were already receiving what many would consider to be optimal therapy for cardiovascular risk reduction: 90% were taking lipid lowering therapy and 70%-75% were taking blood pressure medications with excellent levels of these parameters. On top of this optimal cardiovascular risk therapy, the significant 20% additional cardiovascular risk reduction reported in the SELECT trial is <u>better</u> than adding in treatment with ezetimibe or a PCSK9i to a similar population, both of which are currently approved and covered by Oregon medicaid.[2] Cardiovascular benefits were seen within the first 3 months of therapy and durable for the nearly 4 years of the trial as reported in the supplemental materials in the SELECT trial.[1] This should reassure the committee that this class of drug is complementing existing cardiovascular risk treatments by targeting novel, non-traditional risk factors such as lowering inflammation (hs-CRP) and non-HDL cholesterol.[1]

I would like to comment specifically on the following items:

Plain Language Summary:

1. The use of the term "heart disease" is correct but not complete. The enrollment criteria for SELECT and subsequent FDA indication is broader than this and referred to as "cardiovascular disease." Participants were enrolled who had heart attacks, strokes, and symptomatic peripheral vascular disease affecting blood flow to their legs. While I acknowledge that reading comprehension is important for this part of the report, I would suggest changing to "heart and vascular disease" for improved accuracy.

Proposed prior authorization criteria:

1. Inclusion of approval criteria #19 makes sense in those patients with type 2 diabetes taking Ozempic and who qualify for Wegovy based on BMI criteria, but #20 is out of place since semaglutide 2.0 (Ozempic) is indicated for type 2 diabetes, not the treatment of the disease of obesity. If patients are not already on Ozempic, there is no reason to start a trial of this if they qualify for Wegovy. I would recommend removing it.

Renewal criteria:

1. As I had mentioned in my April 2024 comments, regarding Renewal Criteria #3 and #5 in this version, “stopping” rules have not been applied by the FDA to GLP-1 drugs and are counter to prescribing practices for other chronic diseases. Several clinical scenarios could arise in which weight stability is equally important as I outlined previously. Similar to patients with type 2 diabetes who start off with metformin and then show return of A1c back to baseline, or with hypertension who do not meet therapeutic target with a diurectic, rather than stopping their first-line therapeutic it is best to combine with another medication to augment effectiveness. In treating patients with the disease of obesity as with the treatment of other chronic diseases, I hope to persuade the committee to make these rules “requiring” a formal stop to be reworded as a “recommendation” instead.

2. Including both #3 and #5 is also confusing because it allows for 2 different weight loss thresholds to be applied: at least 1% or less than 5%.

3. Another reason to remove formal stopping rules is that, due to GI tolerability for many patients, safe and effective titration for GLP-1RA’s can mean taking up to 6 months to achieve therapeutic dose. Subsequent determination of maximal weight loss benefit can then take another 6 months to achieve.[3,4] Removing these stopping rules prevents patients from having their therapy halted prematurely.

4. A final reason to remove stopping rules is that the path for a “yes” for criteria #4 should go straight to #6. As mentioned above, the SELECT trial established whether treating patients with Wegovy reduced cardiovascular events and was not constrained by requiring a specific amount of weight loss. Therefore, artificially imposing a stopping rule in the current decision-making algorithm that is based on an arbitrary < 1% or < 5% eight loss does not align with the evidence or FDA guidance, and potentially deny patients the benefit of this medication on future cardiovascular events.

Again, thank you for your consideration and I hope these comments and suggestions can aid in your important work to improve the health and wellbeing of Oregonians.

Sincerely,

Jonathan Q Purnell, MD

References:

1. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med 2023;389(24):2221-2232. DOI: 10.1056/NEJMoa2307563.
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LYFGENIA™ (lovotibeglogene autotemcel) Medicaid Testimony

In response to the committee's unsolicited request for additional information, we provide this information as the committee considers/re-considers the following:

1. Providing access to LYFGENIA to SCD patients through parity positioning on the preferred drug list (PDL)
2. Ensuring the clinical criteria enables access to the most appropriate patient population and is aligned to the LYFGENIA clinical trial protocol

LYFGENIA™ (lovotibeglogene autotemcel), also known as lovo-cel, is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs).[1]

Limitations of Use[1]
Following treatment with LYFGENIA, patients with α-thalassemia trait (-α3.7/-α3.7) may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. LYFGENIA has not been studied in patients with more than two α-globin gene deletions.

Boxed WARNING: Hematologic Malignancy
Hematologic malignancy has occurred in patients treated with LYFGENIA. Monitor patients closely for evidence of malignancy through complete blood counts at least every 6 months and through integration site analysis at Months 6, 12, and as warranted.[1]

Please refer to the full LYFGENIA™ Prescribing Information for additional safety information, including Boxed WARNING regarding Hematologic Malignancy.

Please note that this document includes additional information that may not be mentioned in the LYFGENIA USPI.

Summary

- LYFGENIA's mechanism of action (MOA)
    a. LYFGENIA is a $\beta^{A\text{-}T87Q}$-globin gene therapy consisting of autologous CD34+ cells from patients with sickle cell disease containing hematopoietic stem cells (HSCs) transduced with BB305 lentiviral vector (LVV) encoding βA-T87Q-globin[1]
    b. As an autologous product, LYFGENIA does not require a donor. There is no risk of graft-versus host disease (GvHD) and does not require lymphodepletion during myeloablative conditioning or immunosuppression post-transplant as needed for allo-hematopoietic stem cell transplant (HSCT).[1]
- Baseline characteristics
    a. The lovo-cel clinical trial population included patients with a history of stroke and vasculopathy, patients with chronic pain, as well as individuals with performance scales of Karnofsky/Lansky ≥ 60

- Baseline demographics (N=47) include nearly 6 (13%) of patients with stroke history (8.5% overt stroke and 4.3% silent stroke).[29] There were no reports of strokes after infusion with lovo-cel, including in those patients with a history of stroke assessed via MRI. All patients with a history of stroke remain transfusion independent post-engraftment and stroke-free without recurrent stroke.[29]
- As of February 2023, 30/34 (88.2%) patients (95% CI: 72.5-96.7) achieved complete resolution of all VOEs during the 6 to 18 month assessment period.[29] 100% (10/10) of adolescent patients (≥12 to <18 years) demonstrated complete resolution of VOEs during the 6 to18 month assessment period. During the primary endpoint period (6-18 months), 94.1% (32/34; 95% CI: 80.3-99.3) of patients experienced complete resolution of sVOEs. Furthermore, 85.3% (29/34) of patients had no VOE-related hospital admissions from 6 months post infusion to last follow-up (median follow-up: 36.3 months)

b. Overall baseline characteristics of patients (N=47)
   - Out of 47 patients in HGB 206 Group C and HGB-210, 37 (78.7%) were adults ≥18 years of age, 10 (21.3%) were adolescent; 28 (59.6%) male and 19 (40.4%) female.[29]

c. Longest product exposure was 126.2 patient years of cumulative exposure across clinical trial patients and longest follow-up across HGB-206 Group C and HGB-210 61.0 months (5.1 years).

- Mobilization and Manufacturing
  a. Median mobilization cycles to collect patients was 2 with more than 85% of patients collected in either 1 or 2 cycles total.[28]
  b. Manufacturing timelines (post-cell collection through delivery of drug product) takes about 10-15 weeks but may vary and be up to 150 days.[1,30]

Disease Overview:

Sickle cell disease (SCD) is a rare inherited autosomal recessive red blood cell (RBC) disorder caused by a point mutation in the beta globin gene (HBB). In SCD, production of high levels of sickle hemoglobin (HbS) cause RBCs to become sickled, sticky, and rigid with a shorter lifespan. These abnormal RBCs do not move easily through the blood vessels, leading to the blockage of blood flow which causes painful and potentially damaging sickle cell crises (vaso-occlusive crises) intermittently throughout the patient's life. The abnormal red blood cells (RBCs) also cause a range of serious complications such as stroke, infections, chronic hemolytic anemia, and vasculopathies.[2,3,4]

SCD is a progressive disease with clinical complications occurring and typically worsening throughout the patient's lifetime. Although pediatric patients with SCD may have fewer signs of disease activity compared with adults, organ damage and disease progression begin in infancy.[5,6,7] Many children with SCD experience severe complications within the first 2 years of life, and chronic complications increase in prevalence and severity with age.[8,9,10,11]

Clinically significant events that occur for pediatric patients can cause physiological damage that carries forward into adolescence and adulthood. The lungs of children with SCD are generally more vulnerable to infection, resulting in a high prevalence of bronchial hyperreactivity, asthma, and chronic airway inflammation.[12,13] Bacterial infections with Streptococcus pneumoniae and other atypical microorganisms can lead to ACS in children with SCD, which can create a significant mortality risk as they transition into adolescence.[13,14]

Approximately 50% to 60% of adults with SCD have end-organ disease (e.g., cholelithiasis, cerebral vasculopathy, avascular necrosis, leg ulcers, retinopathy) as a result of chronic complications, with 24% experiencing damage in multiple organs.[15] As multiple organ systems are affected, the risk of mortality increases.

In a recent study, the cumulative risk of cerebral effects, including stroke, silent stroke, abnormal transcranial Doppler scan, and stenosis, is approximately 50% by age 14.[16] Both silent cerebral infarcts and overt stroke are associated with lower cognitive functioning.[17] Even in children without obvious symptoms, underlying hemolysis and endothelial damage can cause "silent" progression of vasculopathy leading to overt vaso-occlusion, chronic end-organ damage, and early mortality .[13] Despite advances in the care of pediatric patients, these chronic complications of SCD typically increase by late adolescence.

The unmet medical need is pronounced in the period of transition from pediatric to adult care when disease driven and environmental factors coincide with a marked increase in disease morbidity and mortality.[8,9,18,19,20] Death is often sudden in patients with SCD, with the leading causes of mortality including pulmonary hypertension, renal failure, infection (including sepsis), thromboembolism, cardiac causes, cirrhosis, pneumonia/ACS, bleeding, and iron overload.[21,22,23]

The epidemiology of SCD has changed dramatically over the years.[24] In the United States, SCD affects approximately 100,000 Americans, occurring among about 1 out of every 365 Black or African-American births and 1 out of every 16,300 Hispanic-American births.[25]

Management of SCD is aimed at avoiding pain episodes, relieving symptoms, and preventing complications.[26]

Overview of LYFGENIA

Mechanism of Action

LYFGENIA is a $\beta^{A\text{-}T87Q}$-globin gene therapy consisting of autologous CD34+ cells from patients with sickle cell disease containing hematopoietic stem cells (HSCs) transduced with BB305 LVV encoding βA-T87Q-globin, suspended in cryopreservation solution. LYFGENIA is intended for one-time administration to add functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into the patient's own HSCs. LYFGENIA is prepared using the patient's own HSCs, which are collected via apheresis procedure(s). The autologous cells are enriched for CD34+ cells, then transduced ex vivo with BB305 LVV. The promoter, a regulatory element that controls the expression of the transgene selected for BB305 LVV, is a cellular (non-viral) promoter that controls gene expression specific to the erythroid lineage cells (red blood cells and their precursors). BB305 LVV encodes $\beta^{A\text{-}T87Q}$-globin. The transduced CD34+ cells are washed, formulated into a suspension, and then cryopreserved.[1]

Cell Collection and Manufacturing

Each patient undergoes HSC mobilization with plerixafor, followed by apheresis to harvest the cells.[1,27] The collected cells are shipped to the manufacturing site where CD34+ cells are selected and then transduced with BB305 LVV to manufacture lovo-cel. In lovo-cel clinical studies, median mobilization cycles to collect patients was 2 with more than 85% of patients collected in either 1 or 2 cycles total.[28] The typical duration of cell collection including mobilization and apheresis is approximately 7 days.[1] Cells are then sent for manufacturing to produce drug product.[27] Once cells have been delivered to the Qualified Treatment Center (QTC), patient is admitted and prepared for myeloablative conditioning with single agent busulfan and infused with LYFGENIA.[1] The transduced HSCs engraft in the bone marrow and differentiate to reconstitute the hematopoietic system, including RBCs with functional Hb containing βA-T87Q-globin (HbA^{T87Q}). Typical manufacturing time takes 10 to 15 weeks, however, can extend up to 150 days for the drug product (DP) to be released after multiple quality control tests.[1,30]

Efficacy and Safety of LYFGENIA

The efficacy of LYFGENIA was studied in a single-arm, 24-month, open-label, multicenter Phase 1/2 study (HGB-206 Group C) and continued on a long-term follow-up study.[1] In HGB-206 Group C, 43 patients underwent apheresis after mobilization with plerixafor of which 36 patients received myeloablative single-agent busulfan conditioning.[1]

The efficacy outcomes were complete resolution of veno-occlusive events (VOE-CR) and severe VOEs (sVOEs) between 6 months and 18 months after infusion with LYFGENIA.[1]

Updates to our clinical trial program efficacy results include an additional 11 patients from our HGB-210 (Phase 3) trial. As of February 13, 2023, among 47 patients who received lovo-cel, the median follow-up time was 35.5 months (3.0 years), overall exposure: 126.2 patient years of cumulative exposure across clinical trial patients and longest follow-up: 61.0 months (5.1 years).

Baseline demographics include nearly 6 (13%) of patients with stroke history [4 (8.5%) overt stroke and 2 (4.3%) silent stroke)].[29] All stroke patients were at least 18 years old and on chronic transfusion therapy prior to lovo-cel infusion. There were no reports of strokes after infusion with lovo-cel, including in those patients with a history of stroke assessed via MRI. All patients with a history of stroke remain transfusion independent post-engraftment and stroke-free without recurrent stroke.

During to 6 to 18 month assessment period, all 34 evaluable patients had stable peripheral blood vector copy number (VCN), total hemoglobin (Hb), and Hb^{AT87Q} after lovo-cel infusion through last follow-up.[29] In total, 30/34 (88.2%) patients (95% CI: 72.5-96.7) achieved complete resolution of all VOEs during the 6-18 month assessment period. 100% (10/10) of adolescent patients (≥12 to <18 y) demonstrated complete resolution of VOEs during the 6 to18 month assessment period. During the primary endpoint period (6 to 18 months), 94.1% (32/34; 95% CI: 80.3-99.3) of patients experienced complete resolution of sVOEs. Furthermore, 85.3% (29/34) of patients had no VOE-related hospital admissions from 6 months post infusion to last follow-up (median follow-up: 36.3 months).[29]

In patients that did not achieve complete resolution of VOEs, hospital admissions were reduced to 0.41 (0, 2) from 2.5 (1, 13) and hospital days were reduced to 2.20 (0.0, 25.4) from 15.75 (3.5, 136.0).[29]

Hematologic malignancy has occurred in patients treated with LYFGENIA (HGB-206, Group A).[1] At the time of initial product approval, two patients treated with an earlier version of LYFGENIA using a different manufacturing process and transplant procedure (HGB-206, Group A) developed acute myeloid leukemia (AML). One patient with α-thalassemia trait (HGB-206, Group C) has been diagnosed with myelodysplastic syndrome (MDS). Patients with sickle cell disease have an increased risk of hematologic malignancy as compared to the general population. The additional hematopoietic stress associated with mobilization, conditioning, and infusion of LYFGENIA, including the need to regenerate the hematopoietic system, may increase the risk of a hematologic malignancy.[1]

Three patients died during LYFGENIA clinical trials; one from sudden cardiac death due to underlying disease and two from acute myeloid leukemia (HGB-206, Group A, as mentioned above).[1]

As of the latest data cut off (February 2023), the majority of treatment-emergent adverse events occurred within 1 year post lovo-cel infusion and were known consequences of conditioning with busulfan.[29] There have been no cases of veno-occlusive liver disease, graft failure, or graft-versus-host disease. Furthermore, there have been no vector-related complications, insertional oncogenesis, or vector mediated replication competent lentivirus.

Please refer to the full US FDA approved LYFGENIA Prescribing Information for additional safety information, including Boxed WARNING regarding Hematologic Malignancy.

Limitations of Use[1]

Following treatment with LYFGENIA, patients with α-thalassemia trait (-α3.7/-α3.7) may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. LYFGENIA has not been studied in patients with more than two α-globin gene deletions.

Boxed WARNING: Hematologic Malignancy

Hematologic malignancy has occurred in patients treated with LYFGENIA. Monitor patients closely for evidence of malignancy through complete blood counts at least every 6 months and through integration site analysis at Months 6, 12, and as warranted.[1]

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