Acentra HEALTH

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2023 Quarter 3 Newsletter

FDA APPROVAL SPOTLIGHT

Veozah (fezolinetant) is a first-in-its-class neurokinin 3 (NK3) receptor agonist approved on May 12, 2023 for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause. Due to hormonal changes in menopause, patients may experience vasomotor symptoms, such as hot flashes and night sweats, most prevalent in the late menopause phase. The pathophysiology for these symptoms is not fully elucidated but the prevailing theories propose that the fluctuation of thermoregulating mechanisms stems from complex interactions of reproductive hormone (e.g. estrogen, progesterone, and testosterone) changes and neurotransmitter mechanisms (e.g. serotonergic, dopaminergic, etc.). Therefore, Veozah's effect targets modulation of thermoregulatory centers in the hypothalamus by antagonizing the binding of neurokinin B (NKB) to its receptor, the kisspeptin/neurokinin B/dynorphin (KNDy) neuron.

Veozah is dosed as one 45 mg tablet once daily by mouth with no dose adjustment necessary for renal dysfunction. It is contraindicated in end-stage renal disease (ESRD), as well as any hepatic dysfunction, including any liver function tests (LFT) at ≥2 times the upper limit of normal (ULN). As it is mostly metabolized in the liver, it is also contraindicated in combination with CYP1A2 inhibitors and cautioned with concurrent inhibitors or inducers of CYP2C19, CYP2C9, and P-glycoprotein (P-gp)/ABCB1. The major adverse effects of concern are increased aspartate aminotransferase (AST), alanine transaminase (ALT), and total bilirubin levels; these require LFT monitoring prior to initiation and at 3, 6, and 9 months of treatment.

SKYLIGHT 1 was a randomized, double-blind, placebo-controlled, phase 3 clinical trial for Veozah performed over 40 weeks at 97 facilities across North America and Europe. The study population (N=522) included women 40-65 years old with an average of ≥7 moderate-severe hot flashes per day. The treatments were assigned as fezolinetant 30 mg once daily, fezolinetant 45 mg once daily, or placebo once daily in a 1:1:1 ratio. The primary outcomes for SKYLIGHT 1 can be seen in Table 1.

Table 1: Primary Outcomes for Skylight 1

Mean Percent Reduction in Least Squares Mean (LSM)	Fezolinetant 30 mg (N=174)	Fezolinetant 45 mg (N=173)
Reduction in VMS frequency at 4 weeks	-1.87 (SE 0.42, p<0.001)	-02.07 (SE 0.42, p<0.001)

Reduction in VMS frequency at 12 weeks	-2.39 (SE 0.44, p<0.001)	-2.55 (SE 0.43, p<0.001)
Reduction in VMS severity at 4 weeks	-0.15 (SE 0.06, p=0.012)	-0.19 (SE 0.06, p=0.002)
Reduction in VMS severity at 12 weeks	-0.24 (0.08, p=0.002)	-0.20 (SE 0.08, p=0.007)

SKYLIGHT 2 was also a randomized, double-blind, placebo-controlled, phase 3 clinical trial for Veozah. It's protocols were identical to SKYLIGHT 1 with the exception that the participants originally assigned to placebo were re-randomized for a full 40-week regimen of Veozah at either the 30 mg or 45 mg doses after the initial 12-week period. The primary outcomes for SKYLIGHT 2 can be seen in Table 2.

Table 2: Primary Outcomes for Skylight 2

Mean Percent Reduction in Least Squares Mean (LSM)	Fezolinetant 30 mg (N=174)	Fezolinetant 45 mg (N=173)
Reduction in VMS frequency at 4 weeks	-1.82 (SE 0.46, p<0.001)	-02.55 (SE 0.46, p<0.001)
Reduction in VMS frequency at 12 weeks	-1.86 (SE 0.55, p<0.001)	-2.53 (SE 0.43, p<0.001)
Reduction in VMS severity at 4 weeks	-0.15 (SE 0.06, p<0.05)	-0.29 (SE 0.06, p<0.001)
Reduction in VMS severity at 12 weeks	-0.16 (0.08, p<0.05)	-0.29 (SE 0.08, p<0.01)

Overall, these results demonstrate the efficacy and safety of both the 30 mg and 45 mg doses of Veozah. As noticed in tables 1 and 2, the efficacy of Veozah is typically as good or better in the reduction of both frequency and severity of VMS symptoms with the 45 mg dose, compared to the 30 mg dose; and both doses are significantly better than placebo at all of the primary outcomes. Due to the unique nature and minor side effect profile of Veozah, it is expected that use of this therapy will become an integral part of treating VMS symptoms in menopausal and postmenopausal patients.

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2023 GUIDELINE UPDATES

With the 2023 peak seasons of influenza, COVID-19, and respiratory syncytial virus (RSV) unfolding, the Advisory Committee on Immunization Practices (ACIP) of the Center for Disease Control and Prevention (CDC) have recently released updated recommendations and guidelines for the prevention of these three diseases through immunization. The importance of maintaining current knowledge and practices on these disease states cannot be overstated, as they pose risk to the population at large while remaining particularly dangerous for high-risk individuals (e.g., older adults, infants, immunocompromised patients, etc.). Described in this article is an overview for the updates to immunization recommendations by ACIP for the prevention of influenza, COVID-19, and RSV.

The influenza season typically lasts from October through May and peaks in November to December. The 2023 updated recommendations for influenza vaccines are shown in Table 1. Notably, everyone of age 6 months or older is still recommended to receive an influenza vaccine ideally from September to October, unless contraindicated. The major difference in the new recommendations is regarding patients with egg allergies as noted in Table 1.

Table 1: ACIP Influenza Vaccination Updates for the 2023-2024 Season

Guidelines Recommendations	2022-2023 Season	2023-2024 Season
Vaccine composition	Update to the influenza A (H1N1) pdm09 component - hemagglutinin (HA) derived from the following: 1.) An influenza A/Victoria/2570/2019 (H1N1)pdm09-like virus (for egg-based vaccines) or an influenza A/Wisconsin/588/2019 (H1N1)pdm09-like virus (for cell culture–based and recombinant vaccines). 2.) An influenza A/Darwin/9/2021 (H3N2)-like virus (for egg-based vaccines) or an influenza A/Darwin/6/2021 (H3N2)-like virus (for cell culture–based or recombinant vaccines). 3.) An influenza B/Austria/1359417/ 2021 (Victoria lineage)-like virus; and an influenza	Update to the influenza A (H1N1) pdm09 component - hemagglutinin (HA) derived from the following: 1.) An influenza A/Victoria/4897/2022 (H1N1)pdm09-like virus (for egg-based vaccines) or an influenza A/Wisconsin/67/2022 (H1N1)pdm09-like virus (for cell culture-based and recombinant vaccines). 2.) An influenza A/Darwin/9/2021 (H3N2)-like virus (for egg-based vaccines) or an influenza A/Darwin/6/2021 (H3N2)-like virus (for cell culture-based and recombinant vaccines). 3.) An influenza B/Austria/1359417/ 2021 (Victoria lineage)-like virus;

	B/Phuket/3073/2013 (Yamagata lineage)-like virus. .	and 4) an influenza B/Phuket/3073/2013 (Yamagata lineage)-like virus.
Egg allergy	Patients with egg allergy should be vaccinated preferentially with a non-egg based formulation. If an egg-based formulation is used, the patient should be supervised in an inpatient or outpatient medical setting by a healthcare provider who is able to recognize and manage severe allergic reactions.	All persons ages ≥6 months can and should receive any influenza vaccine readily available to them, regardless of egg allergy status. These patients do not have to be supervised in an inpatient or outpatient medical setting

In September of 2023, ACIP published a new set of guidelines for the updated COVID-19 vaccine formulations. The newest recommendations are updated to include information on the monovalent Omicron XBB-1.5 variant in a new vaccine formulation (Novavax) to reflect the most common circulating strains. This is a change from the previous formulations of bivalent mRNA, such as from Moderna and Pfizer, that only targeted the original SARS-CoV-2 viral strain and the Omicron variants BA.4 and BA.5. The updated formulations of either the Pfizer or Moderna vaccines are recommended for any person ≥6 months of age, and the Novavax vaccine is recommended for any person ≥12 years of age.

In August and October of 2023, respectively, ACIP updated their recommendations for the prevention of RSV by recommending the use of Beyfortus (nirsevimab) in infants born during the RSV season and children 8-19 months old with high risk of severe disease if infected with RSV and by recommending the administration of the Pfizer RSV vaccine during pregnancy to reduce the risk of lower respiratory tract disease in infants related to RSV.

Due to the individual risks of these three disease states, as well as the similarities in their usual peak seasons, the CDC and ACIP have been regularly compiling evidence and updating guidelines with reference to the prevention of COVID-19, RSV, and influenza infections, particularly targeting high-risk individuals. More information on the supporting literature, full guideline recommendations, vaccination schedules, and patient counseling information can be found on their website.
https://www.cdc.gov/vaccines/acip/index.html

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LEGISLATIVE NEWS

With the overturning of Roe v. Wade in June 24, 2022 (Dobbs v. Jackson Women's Health Organization), access to medication for the medical termination of pregnancy has been a prominent topic of discussion, particularly in primary care and obstetrics/gynecology fields. There are two main medications utilized for this indication, including misoprostol (a prostaglandin) and mifepristone (an antiprogestin and cortisol receptor blocker). These are FDA-approved together as the following two-drug regimen for the termination of intrauterine pregnancies through 70 days of gestation: day 1 – mifepristone 200 mg by mouth; day 2 or 3 – misoprostol 800 mcg buccally (held in place for 30 minutes); day 7-14 – additional dose of misoprostol 800 mcg buccally, as needed following physician assessment.

Particularly in West Virginia, there currently is a total ban on abortion, which includes termination of pregnancy at any stage, except in cases of medical emergency and/or nonmedically viable fetus. This ban includes all procedural and medication-based pregnancy termination methods. Previously, medication-based termination with mifepristone and misoprostol was covered under WV Medicaid, as well as other private payors.

With access to these therapies in question, as well as appropriate and legal methods of prescribing and dispensing, the Food and Drug Administration (FDA) released an update to the risk evaluation and mitigation strategy (REMS) for the use of mifepristone in the termination of pregnancy through 70 days of gestation. Previously, the mifepristone REMS required in-person dispensing, meaning that both parties had to be physically present for the drug to be distributed to the patient. Originally, this was to ensure that appropriate patient counseling was performed and that the patient self-administered the drug correctly. With significantly decreased primary healthcare access, largely due to the COVID-19 pandemic, the FDA dropped this in-person dispensing requirement. Additionally, a requirement was added that any dispensing pharmacy must be certified through the REMS program. Of note, there is currently no REMS program in place for the prescribing of misoprostol.

These changes are important for pharmacists and prescribers, as the dispensing processes have change and patients may have questions regarding these changes. Currently, the updated FDA guidelines allow for dispensing of mifepristone through any certified pharmacy, including mail order pharmacies. Through this process, patients may seek to obtain both mifepristone and misoprostol through out-of-state

providers and pharmacies, despite state-wide bans, such as in West Virginia. Therefore, awareness of current legislation, clinical guidelines/recommendations, and patient education is imperative to ensure safe and appropriate care for these patients.

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