Acentra HEALTH

07/05/23

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2023 Quarter 2 Newsletter

FDA APPROVAL SPOTLIGHT

Zavzpret (zavegepant) was approved on March 10, 2023 as a new intranasal spray for the treatment of migraines with anticipated availability in July 2023. It is intended for the acute treatment of moderate to severe migraines with or without aura in adult patients. This unit-dosed spray is given as 10 mg intranasally at the first sign of pain with a maximum of one dose per 24 hours to prevent medication overuse headache.

Zavzpret's mechanism of action is as a calcitonin gene-related peptide receptor (CGRP) antagonist. Although the exact function of CGRP in migraines is not yet known, it is hypothesized that it influences cerebral vasodilation by binding to receptors on smooth muscle tissue and mast cell release of inflammatory mediators. Zavzpret is unique in this class, as it is the only approved CGRP antagonist that is administered intranasally.
Likely due to its route of administration, Zavzpret was shown to have few systemic effects in clinical trials. Table 1 shows the most common adverse drug reactions (ADRs) that were notes. The most common of these include taste disorders (including dysgeusia and ageusia), nausea, and vomiting. While these did objectively show up more in the treatment group compared to placebo, it is unclear if this is truly a statistical difference, especially in light of the fact that these can be common symptoms of migraines. Additionally, Zavzpret was not studied in high-risk populations, such as pregnancy/lactation and pediatrics, and should be avoided in severe hepatic or renal impairment.

Table 1: Common ADRs Noted in Zavegepant Clinical Trials

Adverse Reaction (%)	Zavegepant (N=1023)	Placebo (N=1056)
Taste Disorders*	18	4
Nausea	4	1
Nasal Discomfort	3	1
Vomiting	2	<1

A phase 2/3 double-blind, randomized, placebo-controlled trial was conducted for Zavzpret in 1673 adults with a migraine at moderate to severe pain. The treatment arms were zavegepant nasal spray at 5 mg (N=387), 10 mg (N=391), 20 mg (N=402), or placebo (N=401). The study concluded that single doses of both 10 mg or 20 mg were both safe and effective for the acute treatment of migraine. Table 2 and Figures 1-2 demonstrate notable efficacy endpoints for this trial.

Table 2: Major Efficacy Endpoints for Zavegepant from Phase 2/3 Clinical Trial

	Zavegepant 10 mg (N=623)	Placebo (N=646)	p-value
Pain Free at 2 hours (%)	147 (23.6)	96 (14.9)	<0.001
MBS Free at 2 hours (%)	247 (39.6)	201 (31.1)	<0.001
Pain Relief at 2 hours	366 (58.7)	321 (49.7)	<0.001
Percentage of Patients Reporting Normal Function at 2 hours	204 (35.8)	152 (25.6)	<0.001
Sustained Pain Freedom from 2 to 48 hours	77 (12.4)	56 (8.7)	0.031

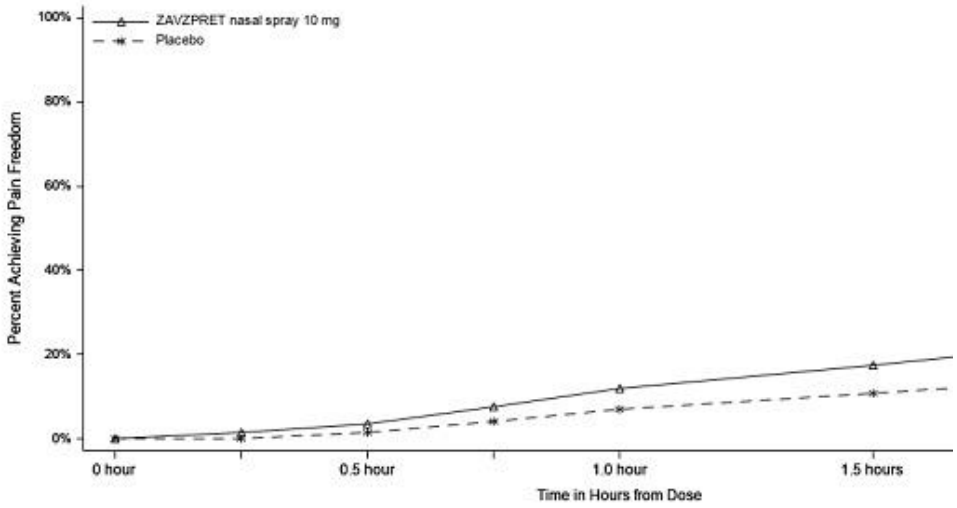

Figure 1: Percentage of Patients Achieving Pain Freedom within 2 Hours in Phase 2/3 Clinical Trial

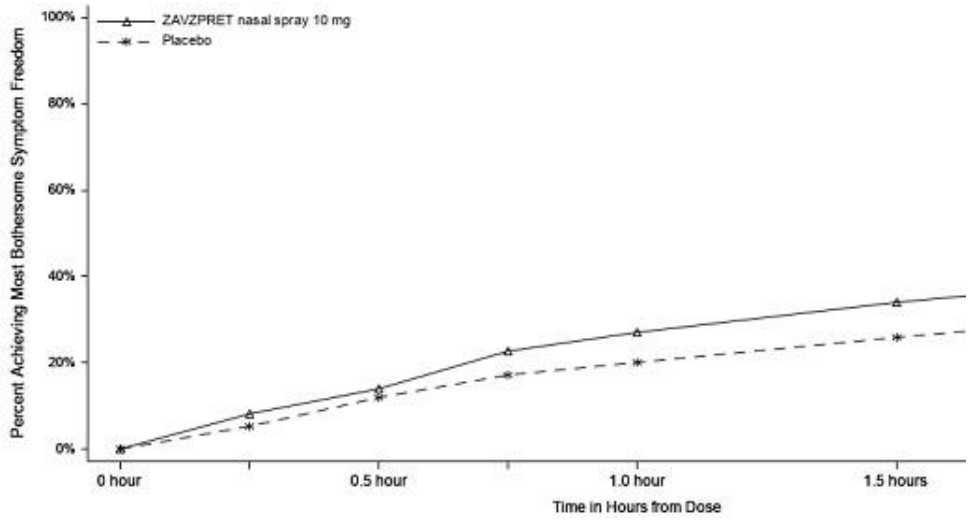

Figure 2: Percentage of Patients Achieving MBS Freedom within 2 Hours in Phase 2/3 Clinical Trial

A phase 3 double-blind, randomized, placebo-controlled trial was conducted to assess the efficacy of Zavzpret in 1269 adults with a history of multiple (greater than 2 but less than 8) migraines with moderate to severe pain per month. The treatment arms were zavegepant 10 mg (N=623) or placebo (N=646). This study concluded that zavegepant nasal spray at a dose of 10 mg was was safe and effective for the acute treatment of migraine in this patient population. Of note, it is unclear whether the participants in the clinical trials had any other preventative or acute treatment therapies during the course of the study, making it very difficult to determine if the effects seen were from the CGRP antagonist mechanism of

action alone. Table 3 and Figures 3-4 demonstrate notable efficacy endpoints for this trial.

Table 3: Major Efficacy Endpoints for Zavegepant from Phase 3 Clinical Trial

	Zavegepant 10 mg (N=623)	**Placebo (N=646)**	**p-value**
Pain Free at 2 hours (%)	88 (22.5)	62 (15.5)	0.011
MBS† Free at 2 hours (%)	164 (41.9)	135 (33.7)	0.016

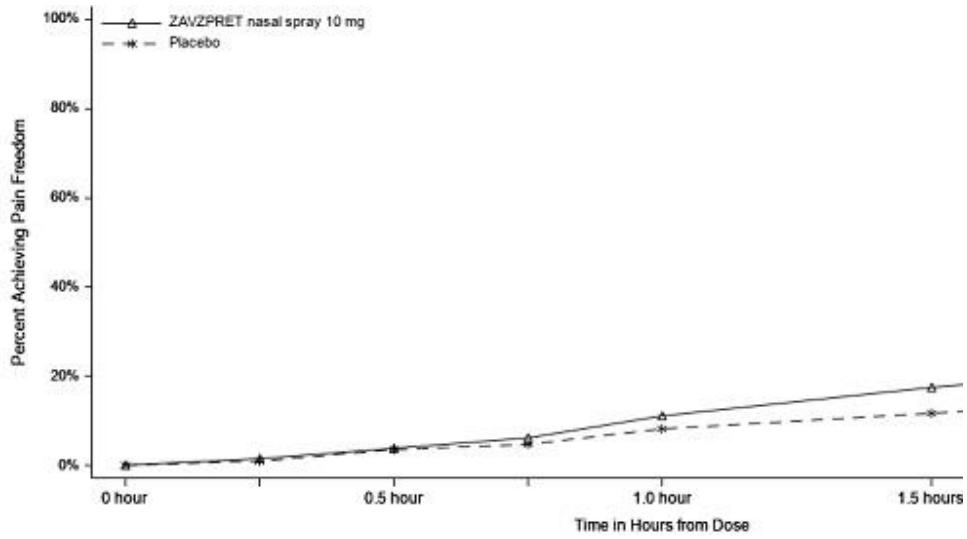

Figure 3: Percentage of Patients Achieving Pain Freedom within 2 Hours in Phase 3 Clinical Trial

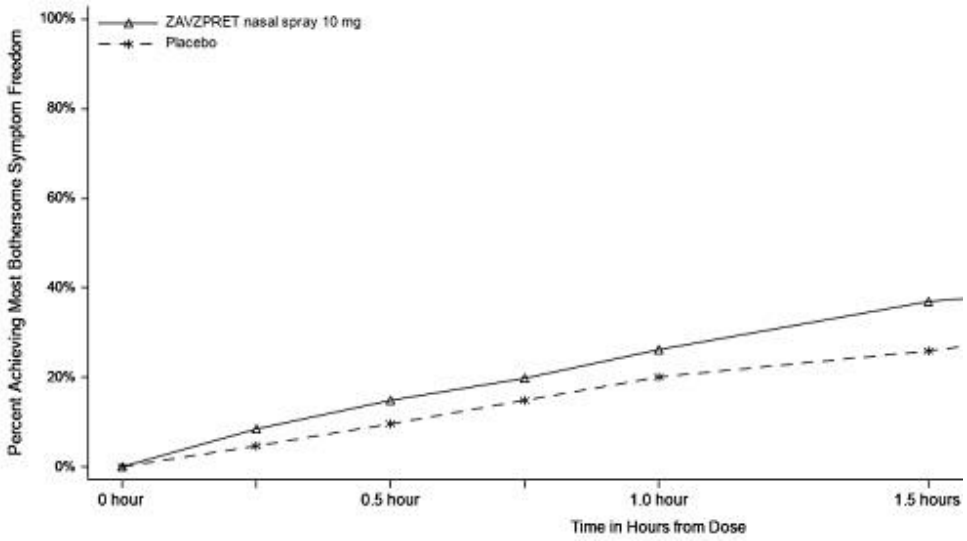

Figure 4: Percentage of Patients Achieving MBS Freedom within 2 Hours in Phase 3 Clinical Trail

Currently, there are no clinical studies comparing Zavzpret to other CGRP agonists or triptans**.** Therefore, it is unclear exactly what its place among comparable therapies will be. Potential benefits for Zavzpret include less systemic absorption and intranasal administration, making this beneficial for patients with needle phobia and/or difficulty swallowing tablets. However, some potential downsides include the fact that Zavzpret is not appropriate for use with concurrent nasal congestion – particularly an issue in patients whose migraines may be triggered by sinus infections, allergies, etc. Overall, it is easy to speculate that with the current safety and efficacy data, Zavzpret has the ability to improve outcomes for patients with moderate to severe migraine as an alternative to oral and injectable CGRP antagonists.

References:

- Zavzpret (zavegepant) [prescribing information]. New York, NY: Pfizer Labs; March 2023.
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2023 GUIDELINE UPDATES

On January 1, 2023, the American Diabetes Association (ADA) published an update to *Standards of Care in Diabetes*, the comprehensive guidelines for the diagnosis and treatment of diabetes and certain common comorbidities. Although these recommendations span almost all aspects of diabetes management, the updates listed in the table below are the most relevant to treatment guidelines and recent pharmacotherapy developments.

Table 4: Summary of 2023 Updates to Standards of Care in Diabetes

Guidelines Recommendations	2022 Standards	2023 Standards
Weight management	Support ≥5% weight loss in patients w/ obesity.	Support 3-7% weight loss in patients w/ obesity to improve glycemia and cardiovascular risk factors. Support >10% weight loss in patients with T2DM and obesity for disease-modifying effect. Prioritize access to anti-obesity drug therapy. Tirzepatide added as an appropriate drug therapy option.
Hypertension definition	Systolic BP ≥140 mmHg. Diastolic BP ≥90 mmHg.	Systolic BP ≥130 mmHg. Diastolic BP ≥80 mmHg.

Pioglitazone use	N/A	Consider use in patients with a history of stroke to lower risk of ACS
Glycemic treatment choice	N/A	Include agents that reduce cardiorenal risk when applicable.
Statin therapy risks	N/A	May increase the risk of T2DM. Monitor blood glucose regularly.
Lipid management	High-intensity statin therapy recommended in patients aged 50-70 years with multiple risk factors for primary prevention of ASCVD. Primary prevention LDL goals: ≥50% reduction from baseline in patients w/ ASCVD risk score of ≥20% Secondary prevention LDL goals: serum LDL <70 mg/dL. Ezetemibe is recommended as addition to statin therapy in this patient population, when necessary.	High-intensity statin therapy recommended in patients aged 40–75 at higher cardiovascular risk for primary prevention of ASCVD. Primary prevention LDL goals: ≥50% reduction from baseline and serum LDL <70 mg/dL. Secondary prevention LDL goals: ≥50% reduction from baseline and serum LDL <55 mg/dL. Ezetemibe or PCSK9 inhibitors are recommended as addition to statin therapy in this patient population, when necessary.
Heart failure management	SGLT2 inhibitor recommended in patients w/ established heart failure reduced ejection fraction.	SGLT2 inhibitor recommended in patients w/ established heart failure with either preserved or reduced ejection fraction.
CKD management	N/A SGLT-2 inhibitor is recommended if eGFR ≥25 mL/min/1.73 m2 or urinary albumin ≥300 mg/g creatinine.	Finerenone is recommended in patients w/ CKD and albuminuria in addition to maximally tolerated ACE-I or ARB therapy. SGLT-2 inhibitor is recommended if eGFR ≥20 mL/min/1.73 m2 and urinary albumin ≥200 mg/g creatinine.

The overall effect of these changes, based on the primary literature references in the updated guidelines, will no doubt lead to improved outcomes in patients with diabetes. By targeting stricter weight, blood pressure, and lipid goals and by honing the management of comorbidities with improved pharmacotherapy, patients will decrease their risk of secondary events and have greater potential for However, newer and higher quantities of drug therapies for most patients with diabetes will come at higher costs to both patients and insurance companies. Pharmacists and prescribers alike must continue assisting patients in improving access to care and treatment to see the purported benefits described above.

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- American Diabetes Association Professional Practice Committee. 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities, 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes, 9. Pharmacologic Approaches to Glycemic Treatment. 10. Cardiovascular Disease and Risk Management, 11. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S39-S45. doi: 10.2337/dc22-S003. PMID: 34964876.
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LEGISLATIVE NEWS

In recent months, actions have been taken to improve access to healthcare for patients with diabetes. Specifically, there are two legislative acts that target insulin prices. These acts combined have the potential to reduce the out-of-pocket costs for insulin in all patients with diabetes, regardless of insurance type, insurance coverage, or type of insulin.

The Inflation Reduction Act of 2022 is in effect as of January 1, 2023. It broadly targets health, tax, and climate change provisions, but specifically mandates improvements in Medicare Parts B and D, drug price negotiation with manufacturers, and inflation rebates. Notably, it allows for a maximum of $35 per month out-of-pocket cost for insulin applicable to Medicare Part B and D patients, as well as a total of $2000 total out-of-pocket cost for any prescription drug per year.

The Affordable Insulin Now Act of 2023 and corresponding Improving Needed Safeguards for Users of Lifesaving Insulin Now (INSULIN) Act of 2023 have been introduced to the U.S. Senate as of March 23 and April 25, respectively, but have

not yet been voted on. In general, these proposed bills seek to expand the cost-limiting effects for insulin from the Inflation Reduction Act of 2022 to all patients, regardless of their Medicare coverage or eligibility. The proposed out-of-pocket cost limitation is the same $35 per month, and this is clarified to include one of each insulin dosage form and type. There are reimbursements included to assist insulin distributors in costs that may exceed $35, particularly for patients that are uninsured.

References:

- The inflation reduction act lowers health care costs for millions of Americans (2022) CMS. Available at: https://www.cms.gov/newsroom/fact-sheets/inflation-reduction-act-lowers-health-care-costs-millions-americans (Accessed: 05 July 2023).
- Inflation Reduction Act of 2022, Pub. L. 117-169, 136 Stat.1818 (Aug. 16, 2022).
- Affordable Insulin Now Act of 2023, S. 954, 118th Cong., 1st Sess. (Mar. 23, 2023).
- Improving Needed Safeguards for Users of Lifesaving Insulin Now (INSULIN) Act of 2023, S. 1269, 118th Cong., 1st Sess. (Apr. 25, 2023).