Category

Best Pharmaceutical Product

General Information

Company Name *

Pfizer Inc.

Product/Solution Name *

ZAVZPRET™

Compound/Tech Name*

Zavegepant

Trade Name *

ZAVZPRET™

Corporate Name *

ZAVZPRET™

Date of Approval *

2023-03-10

Indications *

ZAVZPRET™ (zavegepant) is indicated for the acute treatment of migraine with or without aura in adults. Zavzpret is not indicated for the preventive treatment of migraine.

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Therapeutic Areas *

Neurology

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Attached Files:

- Zavzpret_Pfizer.docx

Background information and need for drug / device
(please be as specific as possible in your description; limit 500 words)

ZAVZPRET™ (zavegepant) has been developed to meet an unfulfilled medical need for patients with migraine who are not well served by existing standard of care agents, including oral triptans and oral CGRP antagonists. Its recent approval in the United States in 2023 has expanded the therapeutic toolbox for this debilitating condition.

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population worldwide. It is characterized by moderate-to-severe episodic unilateral pulsating headaches that, untreated, lasts between 4 and 72 hours. Typical characteristics of the headache include unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. Migraine has a tremendous impact on patients' quality of life and their ability to fulfill family and professional responsibilities. Furthermore, migraine is one of the costliest diseases to society, ranking as the second most costly disease among all diseases including cancer, cardiovascular, and metabolic diseases. Effective and safe treatments for migraine have a significant impact on the well-being of the population worldwide and the productivity of societies, as migraine predominantly affects individuals in their most productive ages.

According to the American Headache Society (AHS), the goals of acute migraine treatment include quick and consistent freedom from pain and related symptoms, especially the most bothersome symptom (MBS), without recurrence, and restored ability to function. In line with these goals, a Delphi study underscores that patients with migraine prefer their acute treatment to alleviate headaches within 30 minutes, prevent worsening of the attack, restore normal functioning within 1 hour, and prevent symptom recurrence on the same day. However, currently available oral or non-oral treatment options may only partially address these treatment goals. Oral treatments such as triptans and oral CGRP receptor antagonists, though often achieving pain efficacy within 2 hours post-dosing, may not offer rapid pain relief within 30 minutes due to limited absorption rates and the need for first-pass metabolism to achieve systemic exposure. A slower onset of effect may be pronounced in patients with nausea/vomiting, gastrointestinal complications, and/or gastroparesis, which are most prevalent in female patients with migraine, accounting for over 75% of all such patients. Furthermore, triptans, regardless of the route of administration (oral or intranasal), may be associated with significant tolerability issues such as somnolence, dizziness, and cardiovascular side effects that prevent patients from returning to normal functioning even when the headache is reduced.

Non-oral migraine treatments are developed with the objective of delivering a rapid onset of treatment effects. Such products are often preferred by migraine patients when an early onset of treatment response is essential, for example, for fast evolving attacks, fully established attacks upon awakening, onset while on duty, or in transit. Patients who have vomiting after oral treatments may also prefer to use a nasal spray for a potentially more reliable relief of their migraine symptoms. Zavegepant nasal spray (ZAVZPRET™) is the first and only intranasal calcitonin gene-related peptide (CGRP) receptor antagonist approved for the acute treatment of migraine.

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History of the development of the solution/product *
(please be as specific as possible in your description; 500 words)

Zavegepant is a third-generation, small-molecule CGRP receptor antagonist. CGRP plays a pivotal role in migraine pathophysiology by dilating cerebral and dural blood vessels, releasing inflammatory

mediators, and transmitting nociceptive signals. Zavegepant is thought to alleviate migraine symptoms by blocking the downstream effects of CGRP signaling. Zavegepant potently inhibits CGRP binding to human CGRP receptors in a concentration-dependent manner, with mean Ki of 23 pM. It shows high selectivity for CGRP receptors over adrenomedullin receptors 1 and 2, calcitonin, and amylin receptors 1 and 3. With excellent aqueous solubility and oxidative stability, zavegepant enables intranasal delivery, with good intranasal bioavailability. Zavegepant dose-dependently inhibited CGRP-induced increases in marmoset facial blood flow and fully reversed CGRP-induced dilation of ex vivo human intracranial arteries. In phase 1 studies, single doses of zavegepant 10 mg nasal spray produced a mean Cmax value associated with 90% inhibition of CGRP signaling. Zavegepant was rapidly absorbed through the nasal mucosa, achieving Tmax of 30 minutes with a t1/2 of 6.55 hours, while allowing it to bypass the gastrointestinal tract and avoid first-pass metabolism.
Zavegepant 10 mg nasal spray is effective in the acute treatment of migraine. A randomized, double-blind, placebo-controlled, dose-ranging phase 2/3 trial evaluated the efficacy of 5, 10, and 20 mg doses. 10 and 20 mg doses were effective, with the 10 mg dose deemed optimal. Efficacy of a single 10 mg dose was confirmed in a randomized, double-blind, placebo-controlled phase 3 trial. In both trials, zavegepant 10 mg was superior to placebo for the coprimary endpoints of freedom from pain and freedom from MBS at 2 hours post-dose. In the phase 3 trial, a between-group difference was seen at the first assessment timepoint (15 minutes post-dose) for both endpoints, and this observed difference vs placebo was maintained throughout the 2-hour testing window. Significantly ($p < 0.05$) more patients in the zavegepant 10 mg nasal spray group than in the placebo group reported improvements in 13 out of 17 secondary endpoints tested hierarchically. Most notably, sustained pain relief from 2 to 24/48 hours, onset of pain relief effect at 15 minutes, and return to normal function at 30 minutes were improved versus placebo.
In a phase 2/3, open-label safety study (n = 603), zavegepant 10 mg nasal spray, used as needed up to eight doses per month for up to 1 year, demonstrated clinically meaningful improvements in migraine-related disability and migraine-specific quality of life among adults experiencing 2-8 moderate to severe migraine attacks monthly. Zavegepant use was also associated with reduced use of analgesics for the acute treatment of migraine.
Zavegepant 10 mg nasal spray was generally well tolerated in clinical trials in patients with migraine, with most common adverse events vs placebo being taste disturbances (18% vs 4%), nausea (4% vs 1%), and nasal discomfort (3% vs 1%). In the randomized phase 3 and phase 2/3 trials, there were no instances of serious AEs or treatment-related serious AEs, and no indication of liver toxicity. The majority of treatment-emergent AEs were of mild or moderate severity.

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Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition *

Zavegepant remains the only approved intranasal CGRP antagonist approved for the acute treatment of migraine and helps address the most important migraine treatment goals: rapid relief of migraine symptoms, rapid return to normal function, sustainable efficacy, and is generally well-tolerated. In controlled trials zavegepant achieved these goals vs placebo with one single nasal spray. As the only novel non-oral product, zavegepant differentiates from other acute pharmacotherapies and offers an alternative option for those patients not well served by existing standard of care or in whom oral

treatment is sub-optimal. Oral agents may not be suitable for many patients due to side effects and/or slow absorption due to comorbidities such as gastrointestinal stasis. Injectable and older intranasal acute treatments such as triptans and dihydroergotamine preparations may have significant side effects and may not be appropriate or convenient for most patients.
Zavegepant represents an important additional therapeutic option for the acute treatment of migraine. For some patients, the nasal spray offers pain relief within 15 minutes of administration, returning to normal function in 30 minutes, and sustained relief for up to 48 hours. It is generally well tolerated, free of CNS side effects, with taste disorders being the most common adverse reaction. Zavegepant nasal spray remains well-tolerated in the long term (when used up to eight times per month for 1 year) with no concerning safety signals. The unit dose spray is small and easy to use and easy to transport in case of attacks outside the home. These clinical results indicate that zavegepant nasal spray aligns with guideline-defined treatment goals and patient preferences and is a unique option to address the unmet medical needs in patients not satisfied with oral medications.
In certain clinical situations, such as in emergency departments or in the workplace, rapid headache pain relief and return to normal function are paramount. Most migraine patients are relatively young and in their most productive stages of life. Disability or functional deficit due to migraine is detrimental to their personal lives, professional aspirations, and productivity. Society is therefore burdened by the consequences when restoration-focused migraine treatments are not utilized. Zavegepant delivers fast onset of action with good tolerability, effectively addressing the need for rapid restoration of patient function and ability to proceed with daily life responsibilities. In addition to the speed of onset, intranasal zavegepant overcomes the limitations of orally administered treatment options in some patients with common gastrointestinal comorbidities of migraine.
In summary, zavegepant combines robust efficacy, good tolerability, and a convenient unit-dose device to deliver an optimized acute treatment that can help address most migraine treatment goals with a single easy-to-use nasal spray. As the only available non-oral CGRP antagonist for acute treatment, zavegepant is unique in this regard and offers an important therapeutic option in the migraine treatment toolbox. This enables individualization of the treatment regimen and allows patients to determine how best to manage their migraine to minimize functional disability and return to their normal function.

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Please provide appropriate references (PubMed, Abstract, Website) *

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