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Review Article

Zavegepant: Revolution To Migraine Therapy

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ABSTRACT

Neurological disorders are a significant concern as they are directly linked to the head controller, whose dysfunctioning results in a major imbalance. Headaches specifically migraine headaches are more alarming and an immediate cure & relief is stipulated to avoid further complications and suffering of humankind. Persistent researches are ongoing for developing targeted approaches for the disease. The Calcitonin gene-related peptide is one of the major potent vasodilators in migraine which opens a curative pathway by use of its antagonist as management options. Zavegepant is a small molecule, CGRP antagonist which specifically targets the neuropeptide & relieves the pain. It shares a novel mechanism of action and its promising clinical trial results have the potential to make a significant breakthrough for those suffering from acute migraine. The review emphasizes the various aspects, and descriptive information related to the newly approved medicinal product & provides a detailed picture along with the groundbreaking successful results of clinical trials.

INTRODUCTION

Migraine is a mysterious disorder characterized with clinical presentations such as pulsating headache and a chronic neurological disorder affecting humans that rules over the world for decades. Migraine affects about one billion people throughout the year and ranked to be the sixth most common leading cause of disability around the world. [1] Migraine headache is one of the common type of headache, arising as one of the main reason of emergency department visits and it accounts to be the 20th most enormously occurring outpatient department visits. Migraine affects 75% of women and 25% of men, predominately affecting females comprising 3:1 incidence, while chronic migraine affects 2% of the global population, which actively interferes with the quality of life of the patients. [2] Migraine has a strong genetic component and various aggravating factors. Migraine is a lifelong disease that results in substantial physical suffering and significant socio-economic impact among individuals, family & peers. Migraine headache is a complex neurobiological disorder specifically characterized

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as unilateral headaches that are often accompanied by photophobia and phonophobia. Migraine is a complex disorder recognized by repetitive episodes of headache, often unilateral and many cases are associated with visual or sensory symptoms collectively termed as an aura that arises most often before the head pain but may also occur during or forward. [3] It is characterized as a unilateral, throbbing, or pulsatile type of headache involving the front temporal & ocular areas typically lasting for 4-72 hours. [1] A migraine attack presents in three phases: premonitory (prodrome), headache phase, and postdrome; each comprising distinctive features which fewer times may be disabling. About 20–25% of migraine patients show symptoms of the fourth phase known as aura. Migraine is often characterized by its activators, usually referred to as triggers. Migraine headaches present with or without an aura. The auras are the sensory symptoms (neurological, autonomic) that may range from flashes of light and blind spots, or tingling sensations in the hands or face, etc.

Several triggering factors result in migraine headaches. Usually, risk factors consist of the ones that are modifiable and others that are non-modifiable. Genetic shows, approximately 70% of patients with migraine have a first-degree relative with a history of migraine. [3] It is strongly genetic that run-in families. Some of the common etiological factors associated with migraine are:

- Hormonal changes, such as mood swings associated with menstruation (common), pregnancy, and ovulation
- Stress, Excessive or insomnia
- Medicines (eg, vasodilators, oral contraceptives)
- Smoking, exposure to sudden flashes of light or fluorescence
- Strong smells or odors (eg, perfumes, petroleum distillates)
- Head trauma. weather changes
- Some others may include stimuli to cold (eg. ice cream) or motion sickness
- Certain foods and additives of food such as caffeine, artificial sweeting agents (eg. saccharin), tyramine containing foods (eg. cheddar cheese) have been suggested as potential precipitants of migraine.

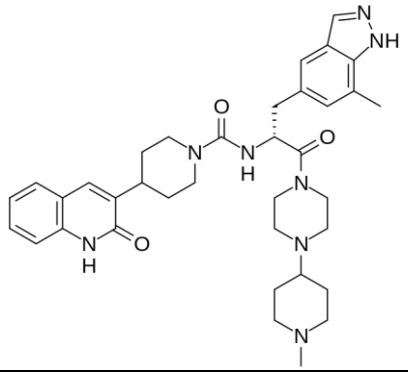
DISCOVERY AND FURTHER HISTORY:

About 40 years back, CGRP therapy was discovered when Amara and other colleagues identified alternative processing of the calcitonin gene.[22] After 5 years, CGRP was identified to have potent vasodilator properties, known to be 10 folds higher than prostaglandins and hundred times higher than other vasodilators such as acetylcholine. In the early 1990s, triptans were explained as inhibiting CGRP release, which is stimulated by trigeminal activation and normalization during migraine attacks, associated with pain. [23] In 1988, the preclinical studies performed on cat models first hypothesized the potential correlation of the neurovascular system in migraine. It showed a spontaneous association between migraine and CGRP. Goadsby et al, after two years, demonstrated some dynamic changes in different concentrations of CGRP in patients with migraine. LASSEN et al, in addition, to make a clear mechanism of CGRP and migraine.[24] the first-generation gepants lifted the worries for liver toxicity and poor oral availability.[25] In December 2019, FDA approved ubrogepant (Ubrelvy®) for the treatment of migraine for people presenting symptoms with and without aura. The second-generation gepants revealed fewer side effects and excellent bioavailability resulting from modifications in molecules. [26] Discussing the third generation gepants is about characterizing variety of routes of administration, the zavegepant [BHV-3500, BMS-742413] was studied for the subcutaneous route and intranasal route of administration due to the pharmacology of the compound.[27] In March 2023, zavegepant

nasal spray [ZAVZPRENTTM] was approved in the USA for the treatment for acute migraine without or with aura in adults. Pfizer, under a license from Bristol-Myers Squibb, zavegepant is being developed as a CGRP receptor antagonist. In middle 2016, Biohaven Pharmaceutical Holding Company entered into a license agreement with BMS for the development and commercialization of zavegapant, as well as other CGRP-related intellectual property. In November 2021, Biohaven pharmaceuticals and Pfizer entered into a collaboration and license agreement. As per the agreement, Biohaven Pharmaceuticals will continue to lead the research and development of zavegepant and Pfizer acquires the right to commercialize zavegepant. The accretion agreement led Pfizer to announce a briefcase of promising CGRP antagonist, ZAVEGEPANT. [6]

PHYSICOCHEMICAL PROPERTIES:

Table No:1: Physico-Chemical Properties Of Zavegepant. [18-22]

Synonyms	• Zavegepant, • Vazegepant, • BMS-742413, • BHV-3500, • Zavegepant [USAN]
Who Atc Code	Antimigraine preparations (N02C)
Chemical Structure	
Hydrogen Bond Acceptors	8
Hydrogen Bond Donors	3
Rotatable Bonds	9
Molecular Formula	$C_{36}H_{46}N_8O_3$
Molar Mass:	638.817 g·mol^{-1}
Iupac Name	N-[(2R)-3-(7-methyl-1H-indazol-5-yl)-1-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-1-oxopropan-2-yl]4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide
Solubility	Freely water soluble, soluble in DMSO
Boiling Point	933.7±65.0°C (Predicted)
Density	1.285±0.06 g/cm^3 (Predicted)

The drug is a newly approved formulation for use in the market, studies are still ongoing and some of the data related to the melting point, UV, and IR absorbance is still unavailable.

CLINICAL TRIALS:

The safety & efficacy of the drug is evaluated through human clinical trials. Clinical trials confirm the safe use of the drug in humans, its action, and how it works. The 2/3 study (NCT03872453), is a double-blind, randomized, placebo-controlled, dose-ranging trial of zavegepant for the acute management of migraine and a trial aimed to find out the optimal dose.[8] The participants were recruited as per the inclusion

criteria which include adults with or above 18 years with two to eight migraine attacks of moderate/severe intensity per month, ≥ 1-year history of migraine with or without aura [defined by the International Classification of Headache Disorders, 3rd edition (ICHD 3)], migraine attacks before age 50 years, and < 15 days per month with migraine or a non-migraine headache within 3 months before screening.[6] The participants who fulfill eligibility criteria were randomized accordingly (1:1:1:1) to zavegepant 5mg, 10mg, 20mg, or placebo. The study included 1581, out of which people received treatment as zavegepant 5 mg (n = 387), 10 mg (n = 391), 20 mg (n = 402), placebo (n = 401) The results of the trial revealed that 10mg & 20mg dose of zavegepant were found more effective than placebo to meet the coprimary terminal point of freedom from pain & MBS (Most Bothersome symptoms) at 2h post-dose. The most bothersome symptoms considered were photophobia (light sensitivity), phonophobia & nausea, which were assessed post-dose using (eCOA) handled device separately. Post-dose status was assessed as absent or present. The intensity of pain was assessed electronically and scored as per the 4-point assessment scale (none, mild, moderate, severe). The study concluded that 10mg & 20mg are effective and safe for use through nasal preparation. [9] The Phase 3 study (NCT04571060), a double-blind, randomized, placebo-controlled, safety and efficacy trial of BHV-3500 (Zavegepant) as a intranasal preparation for the acute treatment of migraine. [10] The inclusion criteria for the study was adult patients above 18 years of age group having a significant history of two to eight moderate or severe migraine attacks per month. Participants were recruited as per the eligibility criteria.1405 participants were eligible, out of which 703 received the active drug zavegepant and 702 received the placebo. The coprimary terminal points were to get relief from pain a score of 0 on a four-point scale as well as relief from the most bothersome symptom (score of 0 on a binary scale) associated with migraine after administration of the first dose post 2h period. [6] The results of the study showed a 2h pain freedom after the treatment dose was more in the participants of the zavegepant group than in the placebo group (24%) vs (15%), a risk difference of 8·8 percentage points with 95% CI 4·5-13·1; p<0·0001) and freedom from their most bothersome symptom was observed (40%) vs (31%), & a risk difference of 8·7 percentage points, 3·4-13·9; p=0·0012) respectively.[11] Zavegepant was found to be efficacious for treatment as acute (abortive) therapy of migraine.

Ongoing trial:

Another study (NCT04804033) a phase 2/3 randomized, placebo-controlled trial, is ongoing to evaluate the safety & efficacy of oral zavegepant for use as preventive therapy for migraine. The dose of 100mg,200mg oral tablet preparation is used in this study. As this is an ongoing study, the results and data related to this is unavailable but it will help evaluate and guide the approval process of zavegepant through nasal as well as oral route.

PHARMACOKINETIC PROPERTIES:

The pharmacokinetics for the newly approved drug zavegepant is available through the preclinical animal studies & clinical human trials performed before the approval. Pharmacokinetics describes the various kinetic changes of drugs in the body. Pharmacokinetics generally gives an idea about the ADME (Absorption, Distribution, Metabolism, Excretion) of a drug described in table no.2. Absorption of zavegepant due to the nasal preparation occurs in the nasal cavity. The peak plasma concentration of the drug is achieved within 30mins after a single 10mg dose administration. The bioavailability of nasal spray formulation is approximately 5%. The distribution phase shows that the drug is highly protein bound. The mean apparent volume of distribution of

intranasal preparation of zavegepant was found to be approximately 1774 L. Zavegepant is majorly metabolized by CYP3A4 enzyme and the minor pathway is CYP2D6 for its biotransformation. Unchanged zavegepant was the found most prevalent (approximately 90%) circulating component in the human plasma when a single IV dose of 5mg was administered. The least considerable metabolites of greater than 10% of the drug were detected in plasma. The elimination half-life (t1/2) for the 10mg intranasal dose of zavegepant is 6.55 hours & mean apparent clearance is 266 L/h. It is excreted mostly via the biliary/fecal route, while the renal route is a minor route of elimination. Excreted via feces ~80%; urine 11%. [13,14] The pharmacokinetic profile also includes drug interaction studies as the drug may interact with other drugs and exert synergistic or antagonistic effect. Zavegepant is a substrate of OATP1B3 and NTCP, concomitant administration with inducers of these transporters may result in decreased zavegepant exposure, whereas the inhibitors of this may increase its serum concentration. Concomitant administration of zavegepant with other intranasal decongestants should be avoided as it may decrease its absorption. [15] Pharmacokinetic interactions of zavegepant exposed to oral contraceptives (ethinyl estradiol) or sumatriptan showed no significant results.

Table No:2: Pharmacokinetic Properties Of Active Drug Zavegepant. [13.14]

PHARMACOKINETIC PARAMETER	VALUE
T max	Approx. 30mins.
Onset of action	Occur as early as 15mins post dose
Absolute bio- availability	Approx 5% for intranasal route
Elimination half-life ($t_{½}$)	6.55 hrs
V_d (Apparent volume of distribution)	1774 L
Protein binding	Highly protein bound ~90%
Metabolism	Hepatic Major pathway- CYP3A4 Minor pathway- CYP2D6
Mean apparent clearance	266L/h
Excretion	Feces ~80% > Urine 11%

MECHANISM OF WORKING:

Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide that reacts on receptors called as calcitonin receptor-like receptors (CLR) which are linked to an activity-modifying protein (RAMP). CGRP is a naturally acting strong vasodilator arising from sensory nerves. For wound healing and cardiovascular physiology, neuropeptide is important component due to its vasodilatory properties. Due to these significant properties, it has its role in various pathways of pain such as migraines where it specifically innervates pain-producing meningeal blood vessels and is released by trigeminal nerve stimulation. [7] CGRP and CGRP receptors are found in the intracranial blood vessel walls, trigeminal ganglion, and dorsal root ganglion with projection in the trigeminal nuclear complex. Fig 1 shows the stimulation of CGRP during migraine. During the headache phase of the migraine this CGRP neuropeptide discharges in the external jugular vein in patients with or without the presence of aura. It is also released when the trigeminal ganglion is stimulated and during

severe migraine attacks. Research has shown that blood CGRP levels are higher in women than in men with a history of migraine. [28]

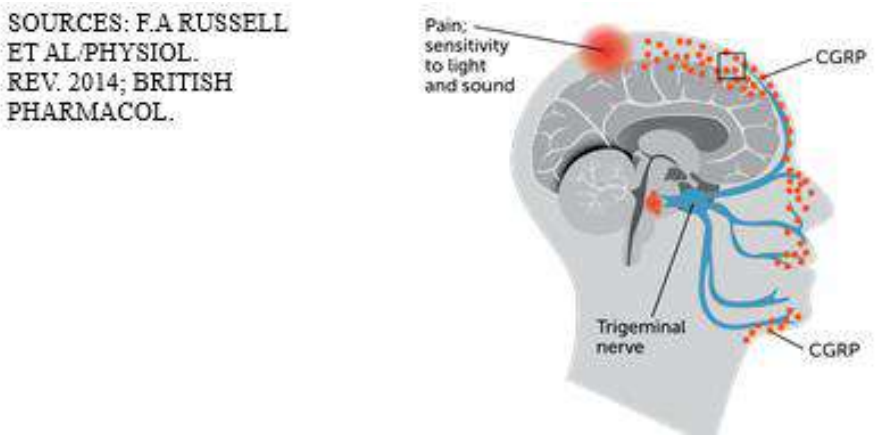


Fig:1: CGRP Stimulation In Migraine [29]

Zavegepant blocks the calcitonin gene-related peptide (CGRP) which stimulates the inflammatory factors and release of migraine-causing factors as shown in Fig 2. It inhibits neurogenic inflammation which is said to be caused by the trigeminal nerve by releasing CGRP. Also, it helps inhibition of dilation of intracranial arteries. Zavegepant also suppresses pain transmission by inhibiting the central relay of pain signals. [29,31]

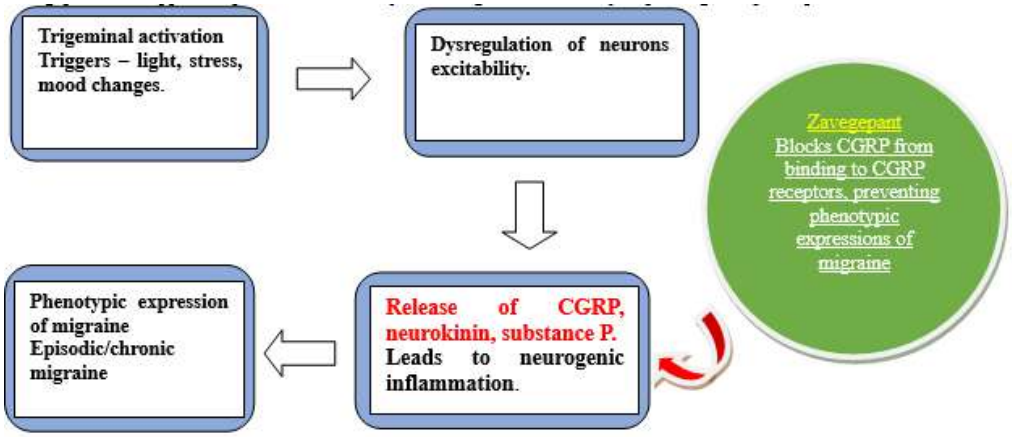


Fig :2: Mechanism Of Action Of Zavegepant

METHODS OF SYNTHESIS:

The synthesis of zavegepant begins with the Horners-Emmons reaction pf trimethylphosphonoacetate with N-Boc-4-piperidone in the presence of NaH in DMF and gives enoate in 92% yield after 3 hours, which is then hydrogenated (55psi) over Pd/C 10% in EtOAc/MeOH to yield saturated ester (94%, 16h), Aldol reaction carried out between ester and o-nitrobenzaldehyde using LDA in THF affords alcohol (94% 4h), upon reductive cyclo-condensation by means of Fe in AcOH at 80 0C furnishes quinoline derivatives (30min, 77%). Dehydration of quinoline derivative with HCL in dioxane/EtOAc provides enone, which is condensed with indazole derivative in the presence of Et3N in DMF to produce urea derivatives (24h, 78%). Saponification of methyl ester with LiOH in THF gives the corresponding carboxylic acid, which is finally coupled with 1-(1-methyl-4-piperidyl) piperazine in the presence of TBTU and

Et3N in DMF(18h, 77%) yields 27% of our target molecule zavegepant. [30]

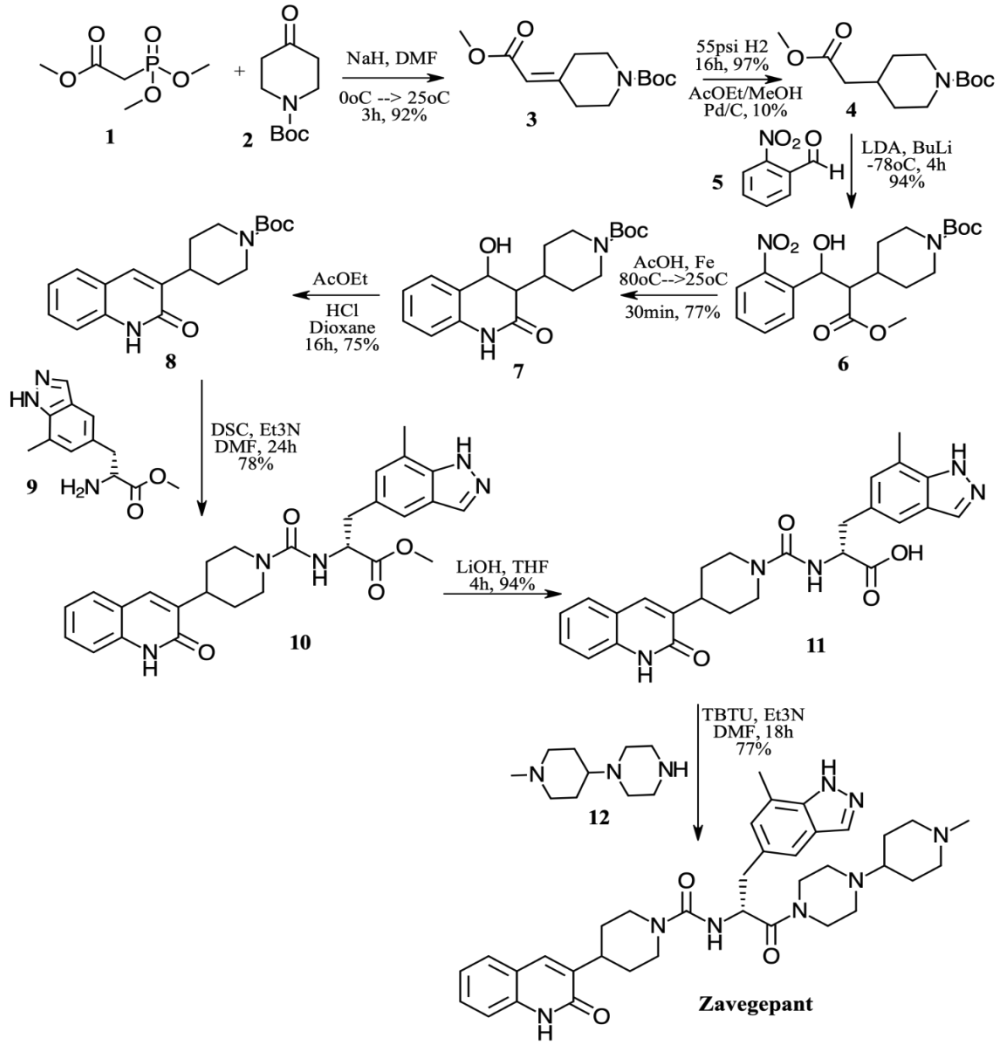


Fig :3: Synthesis Of Zavegepant. [30]

MEDICINAL USES:

Zavegepant is a synthetic, small molecule of calcitonin gene-related peptide receptor antagonist which is a recently approved medicinal product that is well tolerated & effective. The drug is specifically approved as an abortive therapy in migraine with or without aura through extensive clinical trial results. Furthermore, investigations are ongoing for the oral preparation of the drug to be used as a preventive therapy for migraine. A clinical trial regarding the use of the active drug zavegepant in patients with asthma was completed last month in May of this year 2023, but the results related to its safety & efficacy are not published on the official website.[23] The results may clarify its use & may provide the drug another labeled indication for use in respiratory diseases such as asthma. Currently, the drug is only indicated for use in the acute treatment of migraine in adults.[4] Studies of its use in pregnant, breast-feeding women & the pediatric population are not performed yet.

ADVERSE EFFECTS:

Novel agents in the treatment of migraine are always invited and primarily focused on an agent with optimal therapeutic value & minor adverse effects with a greater safety profile. Zavegepant, a novel drug that is a targeted approach, CGRP

antagonist, has a favorable safety profile noticed during therapeutic trials. During the trials, the efficacy of the active drug was compared to placebo, which showed fewer drug-related adverse effects. The commonest adverse effects observed during phase 2/3 & phase 3 studies showed similar results. The adverse effects were relatively mild, which included taste disorders (dysgeusia) [13.5% in 10mg zavegepant vs 3.5% in placebo] in the phase2/3 study whereas dysgeusia was [21% vs 5% in placebo] in the phase 3 study. The other effects were nausea (3%), nasal discomfort (3%), and vomiting. [8,10] Less than 1% of patients had hypersensitivity reactions, including facial muscles swelling and urticaria treated with active drug. [14] It is majorly advantageous over the other drugs in the same class because it shows no signs of hepatotoxicity or elevation of liver enzymes during the studies. [8,10] Hepatotoxicity was a major reason for discontinuation of some 1st & 2nd generation agents of the same class.[16] A study was performed comparing the hepatic safety profiles of newer generation CGRP receptor antagonists to the hepatotoxic CGRP inhibitor telcagepant which confirms that the newer generation CGRP inhibitors are found safer and alone zavegepant showed no ALT (alanine transaminase) elevations at any dose, even though the doses were above the proposed therapeutic doses.[17]This detailed study comparing the safety profiles validates the drug is superior for use over the others in the class of CGRP antagonists.

TREATMENT OF OVERDOSE:

Overdose information related to treatment with zavegepant is still not available. The toxicity studies performed during preclinical animal data is only available, which revealed in vitro, and in vivo, mutagenesis studies for the drug were found negative. Carcinogenesis studies performed for intranasal administration of zavegepant for a dose up to 2.5mg/day to Tgr-asH2, mice up to 26 weeks, showed no signs of tumor growth & similar results were seen for exposure of 18.8mg/kg/day of the drug for a time of 96 weeks which is equal to a highest plasma AUC of 140times the maximum recommended human dose (MRHD). No adverse effects were seen from exposure to the drug during fertility studies. [15,20]

CONTRAINDICATIONS:

Zavegepant is contraindicated in patients who have any episode or history of hypersensitivity to zavegepant or any of its components.[13] No specific contraindications are present through clinical data studies. Hypersensitivity reactions such as facial swelling and urticaria, may occur. If such a reaction occurs, discontinue the use of medication & visit the health care professional, report the event of occurrence, symptoms experienced, and seek further medical care. Continuous pharmacovigilance activities called post-marketing surveillance studies are ongoing since the drug is marketed which helps generate signals.

INTERACTIONS:

Decongestants administered intranasally should not be concomitantly used along with intranasal zavegepant as it may increase the serum concentration of the drug. At least a gap of 1 hour is indicated between two drugs as this is a Risk D interaction which says therapy modification.[13]

As mentioned above, zavegepant is a substrate of OATP1B3 and NTCP transporters therefore, avoid the use of OATP1B1/1B3 (SLCO1B1/1B3) inducers which may decrease the serum concentration of zavegepant; whereas OATP1B1/1B3 (SLCO1B1/1B3) inhibitors are likely involved to increase serum concentration of zavegepant. Pretomanid, voclosporin may increase the serum concentration of zavegepant so therapy monitoring is indicated during its concomitant use. [13,14]

NOVEL MARKETED FORMULATIONS:

Research is continuously emerging in the field of science in the urge to find the best optimal therapy

against a disease. Nowadays, targeted drug therapies are proven to be most effective for providing a proper cure and treatment. Inhibiting the calcitonin gene-related peptide (CGRP) pathway is a new strategic method for migraine prevention & has the potential to improve the quality of life of patients, which may reduce pain sufferings. Calcitonin gene-related peptide is a major potent vasodilator and a key neuropeptide that is a hallway to migraine pathophysiology. It provides greater opportunities for targeted drug response to therapeutically control the migraine attack. Calcitonin gene-related peptide (CGRP) inhibitors block the effect of CGRP, which is involved in pain transmission which rises during a migraine attack. Food and Drug Administration (FDA) approved the first calcitonin gene-related peptide (CGRP) receptor antagonist nasal spray Zavegepant (Zavzpret, Pfizer), for the acute treatment of migraine with or without aura in adults on 9 March 2023 in the USA. [4,5] Zavegepant is a third-generation CGRP antagonist entity, a small molecular size, and highly soluble compound. [6] It is a novel drug that is administered intranasally first in the class of CGRP inhibitors that offers great success as an abortive therapy for migraine. It benefits over the other oral drug formulations used for migraine by providing rapid relief during acute attacks and be a miraculous option for patients who experience severe nausea and vomiting for oral route drugs.

Table No:3: Description Of Novel Formulated Drug.

Brand Name	**Zavzpret**
Image	
FDA Approval	9 March 2023 In the USA
Content	Zavegepant Hydrochloride
Drug Manufacturer	Pfizer Inc**.**
Synonyms	• Zavegepant, • Vazegepant, • Bms-742413, • Bhv-3500, • Zavegepant [Usan]
Who Atc Code	Antimigraine Preparations (N02c)
Formulation Type	Nasal Preparation
Class	Anti-Migraines; Anti-Allergic; Anti-Infectives; Small Molecules; Piperazines.
Pharmacological Class	Calcitonin Gene-Related Peptide Receptor Antagonist
Indication	Use In Adults For Acute Treatment Of Migraine With Or Without Aura
Route Of Administration	Intranasal, Oral (Not Marketed Yet)
Dosage Form	Single Unit Dosage Form, Nasal Spray
Dose	10 Mg Single Spray In 1 Nostril Prn, Not To Exceed 10 Mg/24 Hr. Period.
Dosage Modifications: Renal Impairment: Hepatic Dysfunction:	 If, Crcl ≥30 Ml/Min: No Dosage Adjustment Is Required. Crcl <30 Ml/Min: Avoid Use. Avoid The Use of Zavegepant In Severely Affected Hepatic Function.
Storage Conditions	• Store At Room Temperature Between 68°F To 77°F (20°C To 25°C), Do Not Freeze. • Keep This Medicine and All Medicines Out Of The Reach Of Children.

Price:	G/Act (Per Each): $220.00

PATENT:

Patent WO/2022/217008- Solid State Forms of Zavegepant and Process for Preparation Thereof filed on 8 April 2022. The applicants for the patent are Teva Czech Industries S.R.O [Cz]/[Cz] & Teva Pharmaceuticals USA, Inc. [Us]/[Us]. The inventors are as follows Bártová, Adéla is a researcher in the department of pharmacology; Kolesa, Pavel is a senior manager of physical research & development at Teva Pharmaceuticals; Trčková, Zuzana; Jegorov, Alexandr are the researchers associated with Teva pharmaceuticals. The invention relates to the solid-state forms of zavegepant a 3rd generation CGRP antagonist in crystalline polymorphs its composition & process. The patent's international publication date is 13 October 2022. [31]

CONCLUSION:

The FDA approval of intranasal zavegepant has become a significant milestone in the field of migraine treatment. It offers a unique targeted mechanism, making it the best preference for patients who are unable to tolerate oral triptans or opioid analgesics. Zavegepant, a newer 3rd generation CGRP inhibitor, has the potential to revolutionize care for patients suffering from severe acute migraine attacks. While current alternatives have specific drawbacks & limitations for use in migraine. It is also superior to the other CGRP antagonists and outstands the alarming signs of hepatotoxicity, which is a major concern for other agents in the class. Additional research is ongoing on the use of this drug in other respiratory diseases and the drug is awaited for use as a preventive therapy along with the acute phase of migraine. The intranasal spray offers a safe and reliable solution that can enhance the quality of life and alleviate the debilitating effects of migraines.

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