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LASMIDITIN: A NOVEL THERAPEUTIC OPTION FOR ACUTE MIGRAINE RELIEF IN ADULT

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Abstract:

Receptors on cerebral vessels and induce cerebral vessel vasoconstriction was desired.⁴ Triptans Migraine, a complex and debilitating neurological disorder., second leading cause of disability worldwide. It is characterized by recurrent headaches and a range of associated symptoms, affecting approximately 15% of the population, mostly women. The pathophysiology involves activation of trigeminocervical complex, cortical spreading depression and abnormal brain activity. Disease pathogenesis mainly based on the four phases. Triptans, selective 5-HT_{1B/D} agonists, are first-line treatments for acute migraine but pose cardiovascular risks, which has led to the development of new drug lasmiditan, a selective 5-HT_{1F} receptor agonist that does not cause vasoconstriction. Lasmiditan has shown safety and efficacy in treating migraines, particularly in patient with cardiovascular risk factors. The disease mechanism suggest that migraine attacks begin centrally, with prodromal symptoms indicating hypothalamic involvement. Understanding the interplay between these mechanisms it is crucial to develop different therapies. Detailed information about the drug and its pharmacokinetics, pharmacodynamics, drug interaction).

INTRODUCTION:

Migraine is a complex neuronal process involving activation and sensitization of the trigeminal nociceptors and the trigeminocervical complex, as well as cortical spreading depression and abnormal brain stem activity.^{1,2} Migraine is ranked by the world health organization as the world's second leading cause of disability.³

Triptans, selective 5-HT_{1B/D} agonist, were initially developed when migraine was believed to be a "vascular headache" and triptans ability to activate the 5HT_{1B} and 5HT_{1D} cause vasoconstriction by activation of 5HT_{1B} receptors,^{4,5}

conferring a small risk of serious cardiovascular adverse events.⁶ Triptan are currently a first-line treatment for acute migraine. Triptans are contraindicated in patients with certain cardiovascular conditions and events such as vascular disease, hemiplegic migraine, uncontrolled hypertension, stroke and product label contain warning for patient with cardiovascular risk factors.^{7,8} Because cardiovascular conditions, events and procedure are common in migraine⁹ 30% to 40% of patients with migraine do not respond to triptans,¹⁰ it is reported that 76% of patient taking oral sumatriptans experience heavy arms and

MANUSCRIPT ID: BTS0926004

50% experience chest pressure,¹¹ but this chest pain is non-ischemic. While ischemic events attributable to triptans are uncommon,¹² there are case reports of myocardial infarctions and strokes after initiation of sumatriptans.¹³ non-steroidals, which are also often used for acute migraine treatment, have been associated with increased risk of myocardial infarction.¹⁴

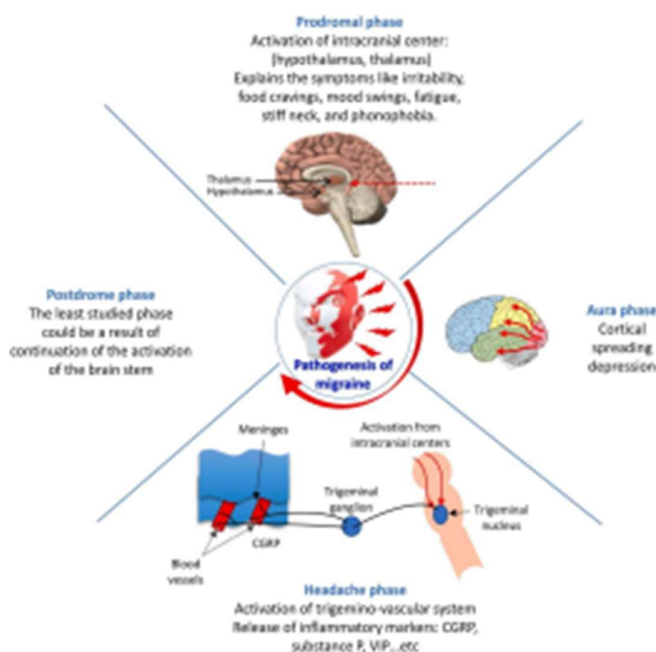
Lasmiditan is high-affinity, highly selective 5HT_{1F} receptor agonist that acts on the trigeminal system without causing vasoconstriction because of its low affinity for 5HT_{1B} receptors.^{3,5} Lasmiditan is being developed as an acute therapy for migraine to support the patient with

cardiovascular risk factors, those with cardiovascular disease, or patient who respond poorly to their current treatment. In a phase 2B study, oral lasmiditan was safe and effective in the acute treatment of

migraine.¹⁵ In this first phase 3, prospective, randomized, double

blind, placebo-controlled study to assess the efficacy and safety of lasmiditan (200 and 100 mg) in the acute treatment of migraine, patients with cardiovascular risk factors were intentionally enrolled. This phase 3 pivotal trial, with a prespecified modified intent-to-treat (mITT) analysis population, was conducted under Special Protocol Assessment with the US Food and Drug Administration (FDA).¹⁶

Pathophysiology of migraine: Pathophysiological understanding of migraine is based upon anatomy and physiology of the pain producing structure of cranium integrated with knowledge of central nervous system (CNS) modulation of these pathways. Migraine is in essence a familial episodic disorder whose key marker is headache with certain associated features (Box 1).

FIGURE1: PATHOGENESIS OF MIGRAINE¹⁷



MANUSCRIPT ID: BTS0926004

BOX 1:

International Headache Society features of migraine

Repeated episodic headache (4 to 72 hours) with the following features:

Any two of:

Unilateral

Throbbing

Worsened by movement

Moderate or severe

Any one of:

Nausea/vomiting

Photophobia and phonophobia

Data from Headache Classification Committee of The International Headache Society. The International classification

Phases of migraine:¹⁷

There are four

phases of migraine that

includes

1) Prodromal phase

2) Aura phase

3) Headache phase

4) Postdrome phase

Migraine is a recurrent headache disorder affecting ~15% of the population during the formative and most productive period of their lives, between the ages of 22 and 55 years.¹⁸ It mainly affects more women than men (3:1 female to male ratio);¹⁹ It frequently starts in childhood, particularly around puberty. In some cases, the headache begins with no warning signs and ends with sleep. In other cases, the headache may be preceded by a prodromal phase that includes fatigue; euphoria; depression; irritability; food cravings; constipation; neck stiffness; increased yawning; and/or abnormal sensitivity to light, sound, and smell,^{20,21} or an aura phase that include variety of focal cortically mediated neurological symptoms that appears just before and/or during headache phase.^{22,23} Symptoms of migraine aura produces both positive (gain-of-function) and negative (loss-of-function), it may present as scintillating lights and scotomas when affecting the visual cortex; parathesia, and numbness of the face and hands when affecting the somatosensory cortex; tremor, unilateral muscle weakness when affecting the motor

cortex or basal ganglia; and difficulty saying words (aphasia) when affecting the speech area (Cutrer and Olesen, 2006). As the headache progress it may be accompanied with variety of autonomic symptoms (nausea, vomiting, nasal/sinus congestion, rhinorrhea, lacrimation, ptosis, yawning, frequent urination, and diarrhea), affective symptoms (depression and irritability) cognitive symptoms (attention deficit, difficulty finding words, transient amnesia, and reduced ability to navigate in familiar environments), and sensory symptoms (photophobia, phonophobia, osmophobia, muscle tenderness, and cutaneous allodynia).^{25,26} The extent of these symptoms suggest that migraine is more than a headache, It is now considered as complex neurological disorder that affect multiple cortical, subcortical, and brainstem areas. As such, it is evident that the migraine brain differs from the nonmigraine brain.²⁷

(1) hypothalamic neurons are in a position to regulate the firing of preganglionic parasympathetic neurons in the



MANUSCRIPT ID: BTS0926004

superior salivatory nucleus (SSN) and sympathetic preganglionic neurons in the spinal intermediolateral nucleus. (Fig. 1A)^{33,34}

In most of the cases, migraine attacks are likely to begin centrally, in brain areas capable of generating the classical neurological symptoms of prodromes and aura, whereas the headache phase begins with consequential activation of meningeal nociceptors at the origin of the trigeminovascular system.²⁸ There is some clues that occurrence of aura can activate nociceptors in meninges exist, but there is no data about the mechanism that prodromes initiates headache phase. Mounting evidence for alterations in brain structure and function that are secondary to the repetitive state of headache can explain the progression of disease.²⁹ Commonly described symptoms by patients are pointing to the potential involvement of the hypothalamus (fatigue, depression, irritability, food cravings, and yawning), brainstem (muscle tenderness and neck stiffness), cortex (abnormal sensitivity to light, sound, and smell), and limbic system (depression and anhedonia) in the prodromal phase of a migraine attack.³⁰ Recently, much attention has been given to the hypothalamus because it plays a key role in many aspects of human circadian rhythms (wake-sleep cycle, body temperature, food intake, and hormonal fluctuations) and in the continuous effort to maintain homeostasis. Because the migraine brain is extremely sensitive to deviations from homeostasis.

The mechanisms by which hypothalamic and brainstem neurons can trigger a headache is central to our ability to develop therapies that can intercept the headache during the prodromal phase (i.e., before the headache begins.³¹ The two different possibilities that are developed are (Fig . 2)

1) hypothalamic neurons that respond to changes in physiological and emotional homeostasis.

It is done by altering the balance between parasympathetic and sympathetic tone in meninges.³² (2) the SSN can stimulate the release of acetylcholine, vasoactive intestinal peptide, and nitric oxide from meningeal terminals of postganglionic parasympathetic neurons in the sphenopalatine ganglion (SPG), leading to dilation of intracranial blood vessels, plasma protein extravasation, and local release of inflammatory molecules capable of activating pial and dural branches of meningeal nociceptors. (3) meningeal blood vessels are densely innervated by parasympathetic fibers (4) activation of SSN neurons can modulate the activity of central trigeminovascular neurons in the spinal trigeminal nucleus (5) activation of meningeal nociceptors appears to depend partially on enhanced activity in the (6) enhanced cranial parasympathetic tone during migraine is evident by lacrimation and nasal congestion and, finally, (7) blockade of the sphenopalatine ganglion provides partial or complete relief of migraine pain. The second proposal suggests that hypothalamic and brainstem neurons that regulate responses to deviation from physiological and emotional homeostasis can lower the threshold for the transmission of nociceptive trigeminovascular signals from the thalamus to the cortex—a critical step in establishing the headache experience. This proposal is based on understanding how the thalamus selects, amplifies, and prioritizes information it eventually transfers to the cortex,^{35,36,37} and how hypothalamic and brainstem nuclei regulate relay thalamocortical neurons.³⁸ It is constructed from recent evidence that relay trigeminothalamic neurons in sensory thalamic nuclei receive direct input from



MANUSCRIPT ID: BTS0926004

hypothalamic neurons that contain dopamine, histamine, orexin, and melanin concentrating hormone (MCH), and brainstem neurons that contain noradrenaline and serotonin. (Fig. 1B,C)³⁹ In principle, each of these neuropeptides/neurotransmitters can shift the activity of thalamic neurons from burst to tonic mode if it is excitatory (dopamine, and high concentration of serotonin, noradrenaline, histamine, orexin), and from tonic to burst mode if it is inhibitory (MCH and low concentration of serotonin). The opposing factors that regulate the firing of relay trigeminovascular thalamic neurons provide an anatomical foundation for explaining why prodromes give rise to some migraine attacks but not to others, and why external (e.g., exposure

to strong perfume) and internal conditions (e.g., skipping a meal and feeling hungry, sleeping too little and being tired, or simple stress) trigger migraine attacks so inconsistently. In the context of migraine, the convergence of these hypothalamic and brainstem neurons on thalamic trigeminovascular neurons can establish high and low set points for the allostatic load of the migraine brain.²⁷

Cortical spreading depression:

Clinical and preclinical studies suggest that migraine aura is caused by cortical spreading depression (CSD), a slowly propagating wave of depolarization/excitation followed by hyperpolarization/inhibition in cortical neurons and glia.^{40,41} While

specific processes that initiate CSD in humans are not known, mechanisms that invoke inflammatory molecules as a result of emotional or physiological stress, such as lack of sleep, may play a role. In the cortex, the initial membrane depolarization is associated with a large efflux of potassium; influx of sodium and calcium; release of glutamate, ATP, and hydrogen ions; neuronal swelling^{42,43} upregulation of genes involved in inflammatory processing; and a host of changes in cortical perfusion and enzymatic activity that include opening of the mega channel *Panx1*, activation of caspase-1, and a breakdown of the blood-brain barrier.⁴⁴ Outside the brain, caspase-1 activation can initiate inflammation by releasing high-mobility group protein B1 and interleukin-1 into the CSF, which then activates nuclear factor- κ B in astrocytes, with the consequential release of cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) into the subarachnoid space.⁴⁴ The introduction into the meninges of these proinflammatory molecules, as well as calcitonin gene-related peptide (CGRP) and nitric oxide,⁴⁵ may be the link between aura and headache because the meninges are densely innervated by pain fibers whose activation distinguishes headaches of intracranial origin (e.g., migraine, meningitis, and subarachnoid bleeds) from headaches of extracranial origin (e.g., tension-type headache, cervicogenic headache, or headaches caused by mild

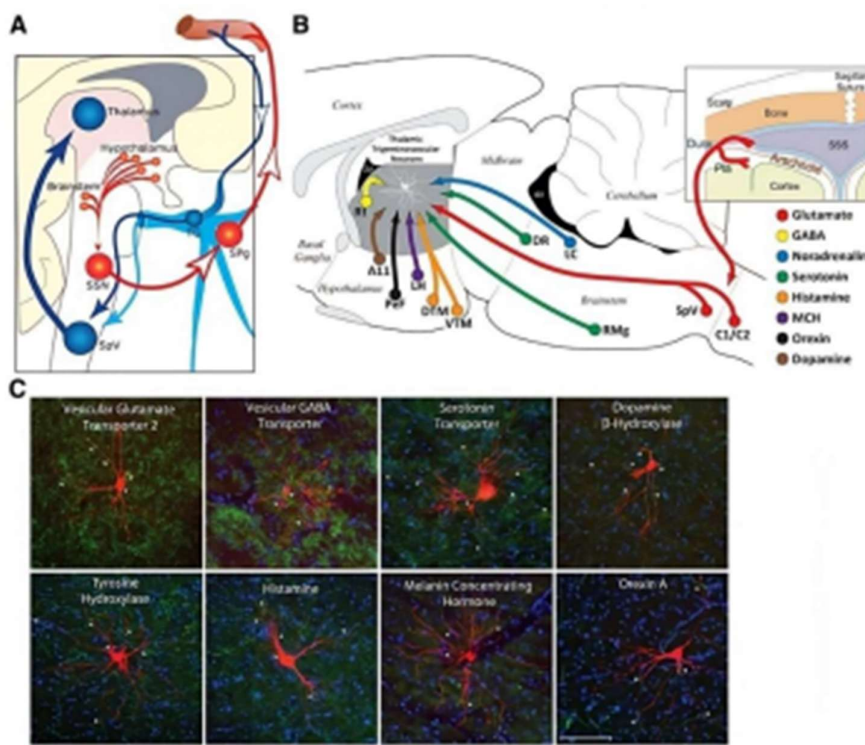


FIGURE 2:

From prodromes to headache: proposed hypothesis for the initiation of headache by the hypothalamus and brainstem. A, Hypothalamic–parasympathetic pathway for the activation of meningeal nociceptors by neurons that regulate homeostasis, circadian rhythms, and autonomic functions (adapted from Burstein and Jakubowski, 2005). Hypothalamically mediated activation of pre-ganglionic parasympathetic neurons in the SSN can trigger the release of acetylcholine, vasoactive intestinal peptide, and nitric oxide from meningeal terminals of postganglionic parasympathetic neurons in the SPG. B, C, Neurochemical pathways capable of modulating the excitability of relay thalamocortical neurons in response to deviation from physiological (food intake, sleep) and emotional (stress, anxiety) homeostasis. The illustration (top right) shows the hypothalamic and brainstem origin of

each of the pathways found to converge on thalamic trigeminovascular neurons (adapted from Kagan et al., 2013; Noseda et al., 2014). The photomicrographs show the extent of innervation by vesicular glutamate transporter, vesicular GABA transporter, serotonin transporter, dopamine beta hydroxylase, tyrosine hydroxylase, histamine, melanin-concentrating hormone, and orexin A. INTRODUCTION TO THE COMPOUND:

Lasmiditan is a drug belonging to the so called ditan family. Lasmiditan is a highly selective 5-HT_{1F} receptor agonist.⁴⁶ For the acute treatment of migraine with or without aura in adults, the U.S. Food and Drug Administration (FDA) approved in October 2019 the first-in-class “ditan”—lasmiditan 50 mg and 100 mg tablets.⁴⁷

CHEMISTRY:



MANUSCRIPT ID: BTS0926004

Lasmiditan belongs to the 4-halobenzoic acids organic compounds class. lasmiditan chemical

IUPAC name is 2,4,6-trifluoro-N-[6-[(1-methylpiperidin-4-yl) carbonyl] pyridin-2-yl] benzamide. It is worth remarking that lasmiditan pyridinoyl-piperidine scaffold has replaced the indolic structure of serotonin (5-HT), peculiar of triptans class (5-HT_{1B}/1D receptor agonists) and other recent 5-HT_{1F} receptor agonists.⁴⁸

PHARMACOLOGY:

Lasmiditan, previously known as COL-144 and LY573144, is a highly selective 5-HT_{1F} agonist. It is selective for the 5-HT_{1F} receptor and its mechanism of action is neuronal without evidence of vasoactive effects. While Triptans non specifically bind to the 5-HT_{1B} and 5-HT_{1D} receptors and with varying affinity bind the 5-HT_{1F} receptors, causing direct vascular vasoconstriction.⁴⁹ In contrast, ditans are selective for the 5-HT_{1F} receptor and its mechanism of action is neuronal without evidence of vasoactive effects. In pre-clinical and clinical models believed to mimic human cerebral and cardiovascular contractility.⁵⁰

MODE OF ACTION:

In the current prevailing theory of migraine pain, trigeminal activation triggers the release of signaling proteins including CGRP, causing secondary cerebral vessel dilation, plasma protein extravasation, and mast cell degranulation.^{51,52} So as triptans are potent 5HT_{1B/D} agonist, they exhibit partial 5-HT_{1F} activity and act upon neuronal pathways.⁴⁹ Using established animal models of migraine, 5-HT_{1F} receptor agonists showed decreased plasma protein extravasation⁴⁹ as well as c-fos expression,⁵³ and suppressed neuronal firing within the trigeminal nucleus caudalis.

Lasmiditan is a highly selective 5-HT_{1F} agonist, having a greater than 450-fold increased affinity for 5-HT_{1F} over 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors. The 5-HT_{1F} receptor is not found on vascular structure and lasmiditan has not shown to have vasoconstrictive effects.⁴⁹

PLASMA PROTEIN EXTRAVASATION

Neurogenic inflammation of the dura is an important cause of migraine pain.⁵⁴ The 5-HT_{1F} receptors are found in high density in the neurons of the trigeminal ganglion. The quantifying protein extravasation from dura mater following painful The following enzymes are not involved in its metabolism: monoamine oxidases, CYP450 reductase, xanthine oxidase, alcohol dehydrogenase, aldehyde dehydrogenase, and Aldo-keto reductases.^{59,60} Unchanged lasmiditan in urine is around 3% of the dose. In contrast, most of the drug is excreted as metabolite S-M8 (66% of the dose), with the majority of recovery within 48 h after administration.^{57,58,59} In patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²), AUC and C_{max} of lasmiditan were 18% and 13% higher, respectively. The recommended single dose

stimulation can be indirectly used to measure the release of pain provoking stimuli (including calcitonin gene related peptide and substance p) from the presynaptic membrane of the trigeminal system. Lasmiditan has been shown to block plasma protein extravasation.⁴⁹

C-fos:

C-fos is a protein that regulates the transcription rate of genes and is used as an indicator of the level of synaptic activation. After painful stimuli, c-fos is measured in high levels within the trigeminal nerve complex.⁴⁹ With repetitive noxious



MANUSCRIPT ID: BTS0926004

stimuli, it is believed that the persistently elevated levels of c

fos trigger long-lasting transcription changes.⁵⁵ 5-HT_{1F} agonists have been shown to decrease c-fos activity within the trigeminal nucleus.⁵⁶ Rats pretreated with lasmiditan have shown decreased c

fos expression in the nucleus caudalis.⁴⁹

PHARMACOKINETICS AND

PHARMACODYNAMICS:

Pharmacokinetics and Pharmacodynamics Upon oral administration, lasmiditan is rapidly absorbed, reaching peak plasma concentrations in a median of 1.8 h.^{57,58,59} Taking the drug with a high-fat meal may prolong the median time to reach maximum plasma concentration (T_{max}) by about one hour and increase its exposure (maximum plasma concentration (C_{max}) and surface area under the concentration–time curve (AUC) by 22% and 19%, respectively). The binding of lasmiditan to blood proteins is 55%–60%, and biological half-life (T_{0.5}) is 5.7h.⁵⁷ The metabolism of lasmiditan is carried out mainly by non-cytochrome P450 (CYP) enzymes hepatically and extrahepatically.

of lasmiditan ranges from 50 mg to 200 mg, depending on pain intensity. As shown for lasmiditan, therapeutic gain for 2 h pain freedom was 15–21% (depending on dose) compared to Ubrogepant (8–10%) and Rimegepant (7%).⁶¹ It is not recommended to take more than one dose a day or drive vehicles up to 8 h after taking the drug. The most common side effects are dizziness, fatigue, paresthesia, and sedation.^{57,58,59,60,61,62,63}

PHARMACOLOGICAL ACTION:

REVIEW ARTICLE

pentazocine selective serotonin reuptake inhibitors, selective serotonin–noradrenaline reuptake

Lasmiditan, a selective 5-HT_{1F} receptor used for acute migraine treatment, primarily affects the central nervous system, with most common side effects being dizziness, somnolence (sleepiness), fatigue, paresthesia (tingling sensation) and nausea; these effects are usually mild to moderate and transient, often resolving within few hours of dosing.^{64,67,69} Unlike triptans, lasmiditan does not cause blood vessel constriction, making it safer for patients with cardiovascular risk factors.^{66,70} Adverse events are more likely at higher doses and in elderly patients, and women may be prone to paresthesia while men experience more

dizziness.^{64,65,68} In rare cases lasmiditan can cause palpitation or malaise but serious adverse effect are uncommon.^{67,64} Importantly, lasmiditan can impair driving and coordination for several hours after use due to its central nervous system effects, so patients are advised not to drive or operate machinery soon after taking it.^{70,64} Beyond its neurological effects, preclinical research suggests lasmiditan may have improving mitochondrial function, but it is only confirmed in animal model so far.⁶⁵ So it concludes that lasmiditan is effective for migraine relief but is associated with higher incidence of central nervous system-related side effect compared to placebo, and caution is advised regarding activities requiring altering of dosing.^{67,69,70}

DRUG-DRUG INTERACTION:

Interaction with serotonergic drugs: Since lasmiditan is a direct serotonin receptor agonist when administered concomitantly with other prescription and over-the-counter drugs or herbal supplements that also increase 5-HT levels the risk of



serotonin syndrome increases.^{57,58,60-63} these drugs are those which increase serotonin formation (e.g., 5-hydroxytryptophan), increase release of serotonin (e.g., mirtazapine), impair serotonin reuptake from the synaptic cleft into the presynaptic neuron (e.g., meperidine, tramadol,

The mechanism involves enhanced absorption and reduced excretion of P-gp substrates due to inhibition of P-gp efflux transporter in the intestine, renal proximal tubule, and liver.⁷² Therefore, administration of lasmiditan with P-gp and BCRP substrate drugs should be avoided.^{57,75,60}

inhibitors, tricyclic antidepressants), inhibit serotonin metabolism by inhibition of monoamine oxidase (MAO) (e.g., MAO inhibitors), and are direct serotonin receptor. In the study of Berg et.al,⁷¹ however, coadministration of lasmiditan and sumatriptan did not cause serotonin syndrome or any clinically relevant interaction between these two drugs. Yet, it is especially important to remember that patients should be carefully monitored for symptoms of serotonin syndrome when doses of ditan and/or other serotonergic drugs are increased.^{57,72,73} Symptoms of serotonin syndrome include mental status changes (coma, hallucination), autonomic dysfunction (tachycardia, hyperthermia), neuromuscular abnormalities. The onset of symptoms usually occurs within minutes to hours of receiving a new or a higher dose of serotonergic agent.⁷² The $T_{0.5}$ should be monitored in the patients as some drugs have extended $T_{0.5}$ and patient may have hepatic dysfunction which prologs $T_{0.5}$ of many drugs. If serotonin syndrome develops during treatment, all serotonergic medications should be discontinued immediately, and supportive care should be given as needed. Severe cases should be managed under consultation with a toxicologist

MANUSCRIPT ID: BTS0926004

and may require sedation, neuromuscular blocking drugs, intubation, and mechanical ventilation.^{72,73}

Interaction with P-gp and BCRP substrates: Lasmiditan exhibited in vitro inhibition of intestinal P-gp and BCRP with drug-drug interaction indices I gut/IC₅₀ (intestinal luminal concentration estimated as dose/250 mL/half maximal inhibitory concentration) of 25 and 16, respectively.⁶⁰ These values exceeded the FDA⁷⁴ cutoff value of 10, indicating that lasmiditan has the potential to inhibit P-gp or BCRP in vivo.⁶⁰ Concomitant use of lasmiditan (perpetrator) and drugs that are P-gp substrates (victims) may increase their blood levels and cause side effects.^{57,75,60}

In vitro studies with the following membrane transporters: multidrug and toxin extrusion proteins (MATE1/MATE2-K), organic cation transporters (OCT1, OCT2), organic anion transporters (OAT1, OAT3), organic anion transporting polypeptide (OATP1B1, or OATP1B3) demonstrated that lasmiditan had a low potential for interactions.^{57,60}

Interaction with heart rate lowering drugs:

It has been shown that in healthy subjects lasmiditan at a single dose of 200 mg, when coadministered with propranolol, could reduce heart rate by additional five beats per minute for a mean maximum of 19 beats per minute compared to propranolol alone.^{76,77}

In vitro studies have shown that lasmiditan has no vasoconstrictive effects at concentrations up to 100 μ M in the rabbit saphenous ring assay which is a reliable predictor of human coronary artery vasoconstrictor liability.⁶⁰ According to the information included in the Summary Product Characteristics of Reyvow, however, lasmiditan in patients taking also heart rate lowering drugs should be used with caution.⁷⁷



MANUSCRIPT ID: BTS0926004

Interaction with CNS depressants: since lasmiditan may result in sedation, other cognitive and/or neuropsychiatric adverse reactions, and driving impairment, it should be used with caution with CNS depressants.^{57,77,60} Lasmiditan is highly lipophilic and capable of penetrating the blood–brain barrier (BBB), hence the most common adverse effects of lasmiditan are CNS-mediated effects such as somnolence and fatigue.^{78,75,69,79}

Potential Effect of Lasmiditan on CYP450 Enzymes:

Lasmiditan is an in vitro inhibitor of CYP2D6. The in vitro sensitivity analyses suggested that increasing lasmiditan inhibition potential by 10-fold increased desipramine or dextromethorphan (sensitive CYP2D6 substrates) AUC values only by 1.2 to 1.3-fold. In other words, the in vivo CYP2D6 inhibition potential for lasmiditan is low.⁶⁰ In vitro studies with other CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8,

Lasmiditan, a newer medication that has been developed provides alternative to the patients by

CYP2C9, CYP2C19, CYP2E1, or CYP3A4), and non-CYP enzymes (MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; FMO3, flavin containing monooxygenase 3) demonstrated that lasmiditan had a low potential for interactions.⁶⁰ It has been shown that lasmiditan does not affect pharmacokinetics of midazolam (CYP3A4 substrate),⁸⁰ caffeine (CYP1A2 substrate),⁸⁰ or tolbutamide (CYP2C9 substrate),⁸⁰ and sumatriptan,⁶⁸ propranolol,⁷⁶ or topiramate.⁷⁹

Summing up, lasmiditan and its metabolites are not clinically relevant inhibitors or

inducers for any of the major CYP enzymes.^{76,79,60,64}

EFFICACY AND SAFETY OUTLOOK:

- Lasmiditan has shown consistent efficacy in both clinical trials and real-world studies, providing pain freedom and relief from bothersome symptoms within 2 hours of dosing
- It is generally well tolerated, with most side effects (dizziness, somnolence, paresthesia) being mild to moderate and decreasing with repeated use.
- Long-term studies indicate sustained effectiveness and no increase in serious adverse events, including cardiovascular events.

CONCLUSION:

As based on the insights provided in this article, migraine is a serious neurological condition that affects the population in their day-to-day life. It is a multifaceted disorder with genetic, neurological, and environmental influences with Complete cure for the disease being unidentified, but it can be controlled by the targeted treatment and management. The first line drug used for the treatment of acute migraine are triptans, acts on 5-HT_{1B/D} receptors, leading to cranial blood vessel constriction and inhibition of pain pathway not recommended to the patients with cardiovascular disease.

targeting a different serotonin receptor and avoiding vasoconstriction. It is the first approved 5HT_{1F} receptor agonist (“ditan”). Lasmiditan represent a significant advance in migraine therapy, especially those who cannot use triptans. It has shown consistent efficacy and providing pain freedom in patients within 2 hours of dosing. Even though lasmiditan is a best alternative in has some side effects which mainly affects the CNS like dizziness,



MANUSCRIPT ID: BTS0926004

fatigue, drowsiness and mild neuropsychiatric symptoms. Lasmiditan is a

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