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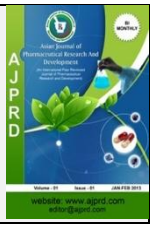

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Review Article

Review: Lasmiditan Drug Discovery for Acute Migraine Treatment

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ABSTRACT

Background: Lasmiditan is a compound developed by Eli Lilly and Company named REYVOW®. Lasmiditan is a highly selective 5-hydroxytryptamine (5-HT1F) receptor agonist, indicated for the treatment of acute migraine with or without aura.

Objective: This review article aimed to discuss the review of the drug discovery of lasmiditan.

Data Source: The author made this review article using the literature study method that is relevant to the purpose of the review. Sources of information from national journals and international journals are accessed through online sites such as Google Scholar, Research Gate, Science Direct, Springer Link, and NCBI. The keywords used to search for journals are Lasmiditan, Migraine, Reyvow®.

Conclusion: Lasmiditan is a highly selective 5-hydroxytryptamine (5-HT1F) receptor agonist, lasmiditan is the only drug approved for the treatment of acute migraine with or without aura whose mechanism of action is specific to the 5-HT1F receptor which has no vasoconstrictive effect.

Keywords: Lasmiditan, Acute Migraine, 5-HT1F

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INTRODUCTION

Drug discovery and development are continuously carried out to continue to produce products that are beneficial in the world of health, pre-clinical trials and clinical trials are important stages in drug discovery and development.[1] The discovery of new drugs aims to treat certain types of diseases that cannot be treated by previously discovered drugs, increase the effectiveness and reliability of drugs, reduce side effects or toxicity, increase drug selectivity, and increase the convenience of drug use.

One of the diseases that many people complain about is migraine. Migraine is a common neurological disease that was the second leading cause of disability among non-fatal diseases in328 diseases from 195 countries between 1990 and 2016.[2]Migraine is an episodic disorder of which headache and nausea are the most characteristic features; others are vomiting and/or a dislike or intolerance to normal levels of light and sound. Headaches are usually moderate or severe in intensity, one-sided and/or throbbing, and exacerbated by routine physical activity; last from hours to 2-3 days. The frequency of attacks is, on average, once or twice a month but can be anywhere between once a year and once a week, often depending on lifestyle and environmental factors that indicate people with migraines react negatively to changes in routine.[3,39]However, the etiology is different. The precise and pathogenesis of migraine is currently unclear. Thus, finding safe, effective and highly specific drugs remains a challenge and requires further research.[4] Currently, many patients use non-specific pain medications to treat migraines such as non-steroidal anti-inflammatory drugs (NSAIDs; for example, ibuprofen or acetylsalicylic acid). Most of these drugs are available over the counter (OTC).[5,36]In patients who do not

benefit from unspecified drugs, triptans or dihydroergotamine (DHE) are widely used.[6] However, triptans show high potency and effectiveness at the 5-HT1B receptor and 5-HT1D that cause direct vascular vasoconstriction.[7,40]This is why triptans are contraindicated in patients with cardiovascular disease, therefore a new class of drugs has been developed, namely "Ditan" whose mechanism of action is specific to the 5-HT1F receptor which has no vasoconstriction effect.

Lasmiditan is a new highly selective 5-hydroxytryptamine (5-HT1F) receptor agonist currently under development for the acute treatment of migraine and is currently the only selective 5-HT1F agonist approved for the treatment of acute migraine.[38] In contrast to 5-HT1B/1D receptor agonists, this substance does not have vasoactive properties in tests predicting human coronary arteries and belongs to the class of antimigraine agents acting on nerves.[8]

Based on this, the authors are interested to study the review of the history of the discovery and development of Lasmiditan to acute migraine treatment. The method used in this review is a literature study. It is hoped that in the future this review can be used as a reference and information by other researchers for the further development of Lasmiditan.

METHODS AND DATA COLLECTION

The author made this review article using a literature study method that is relevant to the purpose of the review. Sources of information from national journals and international journals are accessed through online sites such as Google Scholar, Research Gate, Science Direct, Springer Link, and NCBI. The keywords used to search for journals are Lasmiditan, Migraine, Reyvow®.

RESULTS AND DISCUSSION

LITERATURE REVIEW OF LASMIDITAN

Lasmiditan is a compound developed by Eli Lilly and Company, named REYVOW®, Lasmiditan is 1F receptor agonist serotonin (5-HT) are available orally.[9]Lasmiditan is indicated for the treatment of acute migraine with or without aura but is not indicated for the preventive treatment of migraine.[10]Lasmiditans previously known as COL-144 and LY573144 are highly selective 5HT1F agonists structurally different from triptans.[11]In addition to targeting peripheral 5-HT1F receptors, lasmiditan act centrally as they cross the blood-brain barrier (BBB).[36]This compound is a new drug class that belongs to the “Ditans” class, while the triptans have an indole structure that is very similar to the 5-HT receptor and ditans replace this indole group with a pyridine-piperidine scaffold.[11]

Lasmiditans with the chemical formula C19H18F3N3O2·0.5 [C4H6O4] has the chemical name 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)pyridine-2-yl]benzamide hemisuccinate, whose structural formula can be seen in Figure 1 below.

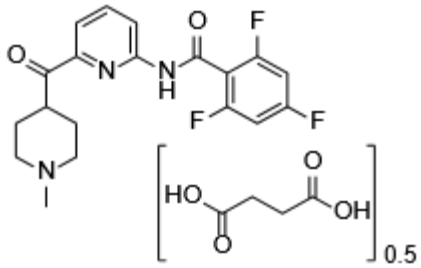

Figure 1: Structure of Lasmiditan

Lasmiditan belongs to the group of organic compounds 4-halobenzoic acid, characterized by the presence of a halogen atom at position 4 of the benzene ring.[12]Lasmiditanhemisuccinate is a white crystalline powder that is slightly soluble in water, slightly soluble in ethanol, and soluble in methanol. The 1 mg/mL aqueous solution of lasmiditanhemisuccinate has a pH of 6.8 at ambient conditions and a molecular weight of 436,41.[13]

Lasmiditan was approved by the Food and Drug Administration (FDA) on October 11, 2019.[9]To represent a new class of migraine drugs, lasmiditan is believed to act both central or peripheral and was developed as an acute treatment for migraine that can address the patient's significant unmet needs, namely cardiovascular risk factors suffered by patients who respond poorly to treatment.[4]

PRECLINICAL TESTING

Pharmacology

Pharmacological processes that occur after lasmiditan administration: Lasmiditan after administration orally, is rapidly absorbed with an average tmax of 1.8 hours and can be affected by concurrent administration of high-fat foods increasing the mean Cmax and AUC lasmiditan values by 22% and 19%, respectively, and delaying the median tmax of 1 hour.[13]Lasmiditan has binding to a plasm protein of 55-60% and is independent of concentration in the range of 15-500 ng/ml.[13]Lasmiditan is metabolized in the liver and excreted in the urine.

In Vitro Test

This test is a preclinical test that uses isolated cell, tissue or organ cultures that are tested outside the body of living things, the results of the research are as follows:

a. Lasmiditan is tested for its functional activity on human 5HT1 receptor clones using the 5HT1 receptor binding method stimulated by [35S]-GTPgS and the results obtained that lasmiditan showed maximum effectiveness at the 5-HT1F receptor which is about 80% and has an effect of 4 times stronger than 5-HT.[7]

b. Lasmiditan blocks the release of CGRP through the 5-HT1F receptor in dura mater samples, trigeminal ganglion and trigeminal caudalis nucleus in rodents.[14]

c. From the results of radioligand studies, it was stated that lasmiditan works selectively to bind the 5-HT1F receptor which indicates that lasmiditan does not have contractile properties in human blood vessels.[15]

In Vivo Test

a. This test is a preclinical test that is carried out in living things, the results of the research are as follows:

b. Lasmiditan inhibits c-fos expression induced by mice trigeminal nucleus caudalis at a dose of 3 mg/kg orally with a time of 1 hour.[7]

c. Lasmiditan inhibits neurogenic dural vasodilation in response to CGRP induced, capsaicin and periarterial electrical stimulation starting from the lower dose; this effect occurs due to the selective activation of the 5-HT1F receptor.[14]

Toxicity Test

This test is a preclinical test to determine the potential of a compound as a poison or to see the toxic effect caused by the compound on biological systems, the results of the research are as follows:

a. Tests have been carried out on rats and dogs on the first selective 5-HT1F receptor agonist (LY334370) and it was found that LY334370 caused toxicity, therefore development was stopped and then replaced by a new generation of Lasmiditan (LY573144) which has a higher level of selectivity than LY334370 and does not cause toxicity.[16,17]

b. In Sprague Dawley rats, frequent oral administration of lasmiditan causes significant cutaneous allodynia in either the periorbital or hind paw and resolves after discontinuation of the drug.[18]

Carcinogenesis Test

This test is a preclinical test to determine whether a substance when used long-term will be able to cause carcinogenic effects, the results of the study are as follows:

Lasmiditan was administered orally to TgRasH2 rats at a dose of up to 150 (male) or 250 (female) mg/kg/day for 26 weeks or to rats at a dose of up to 75 mg/kg/day for 2 years and the results were no tumor due to drug administration.[13]

Teratogenesis Test

This test is a preclinical test to determine the toxic effect of a compound on the fetus, the results of the research are as follows:

In pregnant rats during organogenesis, lasmiditan was administered orally (0, 100, 175, or 250 mg/kg/day) resulted in increased skeletal variation at moderate and high doses and decreased fetal weight at high doses. High doses are associated with maternal toxicity. At a dose of no effect (100 mg/kg/day) for adverse effects on embryofetal development in mice, plasma exposure (AUC) is approximately 10 times that in humans in MRHD.[13]

CLINICAL TEST

PHASE I

The Phase 1 trial is a clinical trial conducted in healthy humans to determine the safety, pharmacokinetic and pharmacodynamic aspects of the drug, the results of the study are as follows:

a. In a proof-of-concept study, Lasmiditan was administered intravenously (iv) to 88 patients at a dose between 2.5-45 mg and was discontinued at 20 mg because it was superior to placebo for treating acute migraine, lasmiditan was well tolerated and there were no serious side effects.[8]

b. In a single-center, open-label, fixed-sequence method in healthy subjects designed to evaluate cardiovascular effects and PK of giving oral lasmiditan 200 mg with 80 mg propranolol 2 times a day in a fasting state involving 44 healthy subjects and getting the results that co-administration of lasmiditan with propranolol decreases heart rate and pulse compared to propranolol alone. Meanwhile, cardiovascular parameters returned to predose levels within 3 hours and heart rate remained significantly low for 12 hours post-dose. But at least observations show the minimal cardiovascular activity of lasmiditan.[19]

c. In a crossover study involving healthy men and women aged 18 to 55 years with a body mass index of 18 to 32 kg/m2 assessing the abuse potential of lasmiditan at doses of 100, 200, 400 mg on recreational polydrug adults compared with placebo with alprazolam 2 mg as a positive control, the results showed that lasmiditan had a higher potential for abuse than placebo.[20]

d. In a randomized, blinded, placebo, and active control crossover study involving healthy adult volunteers, the results showed that the dose of lasmiditan showed significantly driving compared to placebo at 1.5 hours post-dose and impaired driving are not clinically significant at 8, 12, or 24 hours post-dose.[21]

PHASE II

Phase II trials are further clinical trials for drugs that have gone through phase 1 trials that aim to determine the effectiveness of drugs in patients involving hundreds of patients, the results of the study are as follows:

a. In a randomized, multicenter, placebo-controlled study with 130 subjects who were hospitalized with subjects given intravenous doses of 20 mg or more, lasmiditan was shown to be effective in the treatment of acute migraine.[22]

b. In a multicenter, double-blind study, parallel-group, dose range in 43 medical center in five European countries, patients with migraine with and without aura who were not taking prophylaxis were randomly assigned (1:1:1:1:1) to treat one moderate-to-severe migraine attack at doses of lasmiditan 50 mg, 100 mg, 200 mg. mg, or 400 mg, or placebo at 2 hours post-dose and the results showed that lasmiditan reduces the headache response more than placebo.[23]

PHASE III

This trial is a follow-up clinical trial for drugs that have gone through phase 2 clinical trials aimed at determining the effectiveness of the drug.

a. The study was conducted using a randomized method (1:1:1) with double-blind doses of oral lasmiditan 200 mg, 100 mg, and placebo and obtained results from 1856, 77.9% of patients had 1 cardiovascular risk factor

other than migraine. Lasmiditan was shown to relieve headaches more in patients with a dose of 200 mg compared to placebo after 2 hours of administration. Furthermore, it was proven that more patients were free of MBS after administration of lasmiditan 200 mg and 100 mg compared to placebo at 2 hours post-dose.[24]

b. The next study was the same method as the previous phase 3 study, namely the randomized method with a ratio (1:1:1:1) involving 3005 migraine patients with and without aura using oral lasmiditan 200 mg, 100 mg, 50 mg, or placebo, and the results were consistent with the previous phase 3 studies and found some CNS-related side effects such as dizziness, drowsiness, and paresthesias.[25]

c. The next research used 2 phase 3 clinical trials namely SPARTAN and SAMURAI, SPARTAN and SAMURAI was a randomized, double-blind, placebo-controlled trial investigating a single migraine attack involving 5236 patients. SAMURAI evaluated 2 doses and SPARTAN evaluated 3 doses then data were collected every 30 minutes up to 2 hours after a dose of lasmiditan. The aim of this study was to initially assess the efficacy of lasmiditan and to obtain results at 30 minutes that lasmiditan had demonstrated a benefit against migraine and achieved freedom from MBS over placebo. Overall, treatment with lasmiditan resulted in an earlier onset of efficacy than placebo.[26]Further trials were conducted to assess the efficacy and safety of a second dose of lasmiditan for the acute treatment of migraine and demonstrated that there was no clear benefit from a second dose of lasmiditan for salvage treatment.[27]

d. Further studies assessed the safety of lasmiditan with the SAMURAI and SPARTAN methods and obtained the results that the side effects that emerged from the treatment were generally mild to moderate, the side effects were dizziness, paresthesias, drowsiness, fatigue, nausea, muscle weakness, and hypoesthesia. This is because lasmiditan is a central penetrant drug and is associated with neurological treatment.[28] Then 5 post hoc analyzes of the results of the SAMURAI and SPARTAN phase 3 test data were performed. The first was to assess the characterization of dizziness after the use of lasmiditan and it was found that the incidence of dizziness increased with dose. Dizziness is generally mild or moderate in severity and rapid onset and short duration and the presence of dizziness do not affect the efficacy of the drug.[29] The second was to assess lasmiditan for the treatment of acute migraine in patients with cardiovascular risk factors (CVRF) and it was found that the presence of CVRF had no effect on the efficacy of lasmiditan.[30] The third was to assess improvement in function after lasmiditan treatment and found that all doses of lasmiditan resulted in a significant improvement in migraine-associated functional disability.[31] And a subsequent post hoc analysis to evaluate the effectiveness of 2 hours post-dose of lasmiditan for acute treatment migraine attacks that are difficult to treat and result in lasmiditans being an effective alternative to the historically difficult-to-treat type of migraine headache.[32] The last post hoc analysis was to analyze the subgroup with previous responses to triptans and menus, it demonstrated that lasmiditan showed good efficacy and in those with inadequate response to previous triptan therapy as well as in those who were triptan-naive.[33]In pediatric patients from the US and Japan weighing 15 kg to 40 kg for a single dose of 100 mg and >40 kg up to 55 kg for a single dose of 200 mg lasmiditan, it was well-tolerated.[37]

PHASE IV

This test is a clinical trial for a drug that has passed through three phases that aims to see the effectiveness of drugs and drug side effects in the long term, the research results are as follows:

By using the GLADIATOR study method which is an ongoing, prospective, randomized, open-label study of lasmiditan taken intermittently as needed for up to 1 year in patients completing one of the randomized phase 3 studies of SAMURAI and SPARTAN.[34] This study stated that long-term intermittent dosing of lasmiditan is generally safe and well-tolerated for acute migraine and consistent efficacy at the population level quarter to 1 year. The MIDAS assessment to analyze migraine disability showed that there was a progressive and clinically significant reduction in migraine-associated disability during long-term dosing with lasmiditan.[34,35]

LASMIDITAN BIOSYNTHESIS

Biosynthesis is an enzyme-catalyzed process in living organisms, in which substrates are converted to products that normally have a more complex structure. The biosynthetic pathway of lasmiditan consists of 6 steps of synthesis using transfer hydrogenation conditions.[41] Figure 2 below is the biosynthetic pathway of lasmiditan.

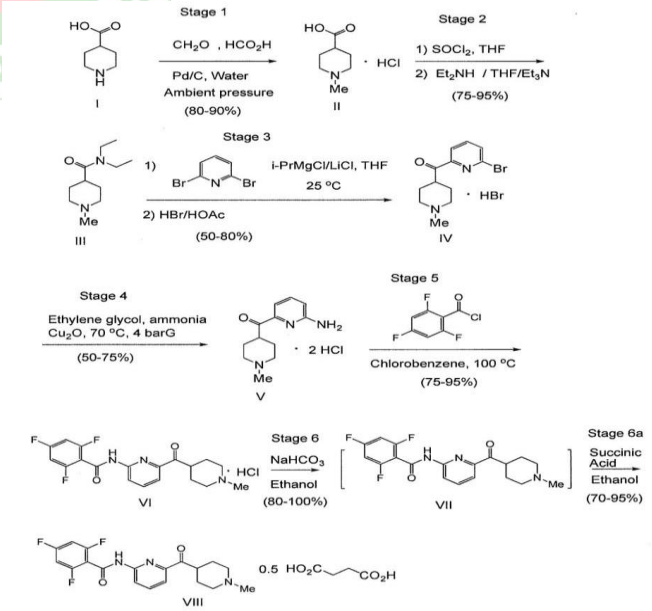

Figure 2: Lasmiditan biosynthetic pathway

Process for preparing 2,4,6-trifluoro-N-[6-(1 methyl-piperidine-4-carbonyl)-pyridine-2-yl)-benzamide or its pharmaceutically acceptable salt. For example, a hemisuccinate salt comprising the step of converting piperidine-4 carboxylic acid (1) to 1-methylpiperidine-4-

carboxylic acid (II) or a salt thereof (for example, to the hydrochloride salt) using transfer hydrogenation conditions. In some embodiments, the invention is directed to a process for preparing 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridine-2-yl]-benzamide hemisuccinate salt comprising the steps as follows: reacts piperidine-4-carboxylic acid (1) with formaldehyde under ambient pressure to produce 1-methylpiperidine-4-carboxylic acid (II).[41]

FORM AND DOSAGE THAT ARE SOLD IN THE MARKET

REYVOW® tablets (Lasmiditan) are available in two dosages:

a. 50 mg tablets with the following characteristics: light gray, oval, film-coated, which is marked with “L-50” on one side and “4321” on the other side of the tablet.

b. 100 mg tablets with the following characteristics: light purple in color, oval, film-coated, marked with “L-100” on one side and “4491” on the other side of the tablet.[13]

CONCLUSIONS

Lasmiditan is a novel highly selective 5-hydroxytryptamine (5-HT1F) receptor agonist, lasmiditan is believed to act both centrally and peripherally and was developed as an acute treatment for migraine that can address the patient's significant unmet needs, namely the cardiovascular risk factors suffered by the patients who respond poorly to treatment.

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