WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL RESEARCH

Review Article

Coden USA: WJPPCL

2026
Volume: 03
Issue: 03
Page: 20-31

A COMPARATIVE ANALYTICAL STUDY OF LASMIDITAN BY UV SPECTROSCOPY, HPLC, AND LC-MS/MS METHODS

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Received: 21 January 2026 **Revised: 02 February 2026** **Accepted: 22 February 2026**

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ABSTRACT

Lasmiditan is a novel, centrally acting selective 5-HT_1F receptor agonist approved for the acute treatment of migraine with or without aura. Unlike triptans, it does not cause vasoconstriction, making it a safer therapeutic option for patients with cardiovascular risk factors. Chemically, lasmiditan is 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-pyridin-2-yl] benzamide with a molecular formula of $C_{19}H_{18}F_3N_3O_2$ and molecular weight of 377.367 g/mol. It is available as lasmiditan hemi-succinate in 50 mg film-coated tablets. Lasmiditan exerts its antimigraine effect by selectively activating central 5-HT_1F receptors located on trigeminal neurons, thereby inhibiting calcitonin gene-related peptide (CGRP) release and suppressing nociceptive transmission within the trigeminovascular pathway. The drug demonstrates rapid oral absorption, moderate protein binding, central nervous system penetration, hepatic non-CYP metabolism, and an elimination half-life of approximately 5–7 hours. Common adverse effects include dizziness, fatigue, somnolence, and paresthesia. Various analytical methods such as UV–Visible spectroscopy, HPLC, RP-HPLC, and LC-MS/MS have been developed and validated for its quantitative estimation, demonstrating high linearity, accuracy, and precision. This review highlights the physicochemical properties, pharmacodynamics, pharmacokinetics, mechanism of action, therapeutic uses, adverse effects, and analytical methods of lasmiditan.

KEYWORDS: Lasmiditan, 5-HT$_1$F receptor agonist, Ditans, Migraine, Pharmacokinetics, Pharmacodynamics, HPLC, LC-MS/MS, UV Spectroscopy.

1. INTRODUCTION

Migraine is a chronic neurovascular disorder characterized by recurrent episodes of moderate to severe headache often accompanied by nausea, photophobia, and phonophobia. Traditional antimigraine therapies such as triptans act primarily through 5-HT$_1$B/1D receptor activation and are associated with vasoconstrictive effects, limiting their use in patients with cardiovascular diseases.

Lasmiditan represents a new class of antimigraine agents known as “ditans.” It selectively targets 5-HT$_1$F receptors located predominantly in the central nervous system and trigeminal pathways. By avoiding activation of vascular 5-HT$_1$B receptors, lasmiditan provides effective migraine relief without causing vasoconstriction. This distinct mechanism enhances its safety profile, particularly in patients with contraindications to triptans.

In addition to its therapeutic importance, lasmiditan possesses defined physicochemical characteristics that support oral administration. It is moderately soluble in DMSO, sparingly soluble in water, and exhibits UV absorbance due to its aromatic and heterocyclic functional groups. Multiple analytical methods including UV spectroscopy, HPLC, RP-HPLC, and LC-MS/MS have been validated for its routine quantitative estimation in pharmaceutical formulations.

Understanding the pharmacodynamics and pharmacokinetics of lasmiditan is essential for optimizing its clinical use. The drug demonstrates rapid absorption, effective CNS penetration, minimal CYP-mediated interactions, and renal excretion primarily as inactive metabolites.

1.1 UV–VISIBLE SPECTROSCOPY:

UV–Visible spectroscopy is one of the most widely used analytical techniques in pharmaceutical analysis for the quantitative estimation of drugs. It is based on the absorption of ultraviolet or visible radiation by molecules, resulting in electronic transitions between molecular orbitals. Compounds containing chromophores such as aromatic rings, conjugated double bonds, and heterocyclic structures exhibit characteristic absorbance in the UV region.

The technique follows Beer–Lambert's law, which states that absorbance is directly proportional to concentration within a specific linear range. Due to its simplicity, cost-effectiveness, rapid analysis, and minimal sample preparation, UV spectroscopy is extensively employed for routine quality control and assay of pharmaceutical formulations. It is particularly useful when the drug molecule possesses suitable UV-absorbing functional groups, enabling accurate and precise quantification.

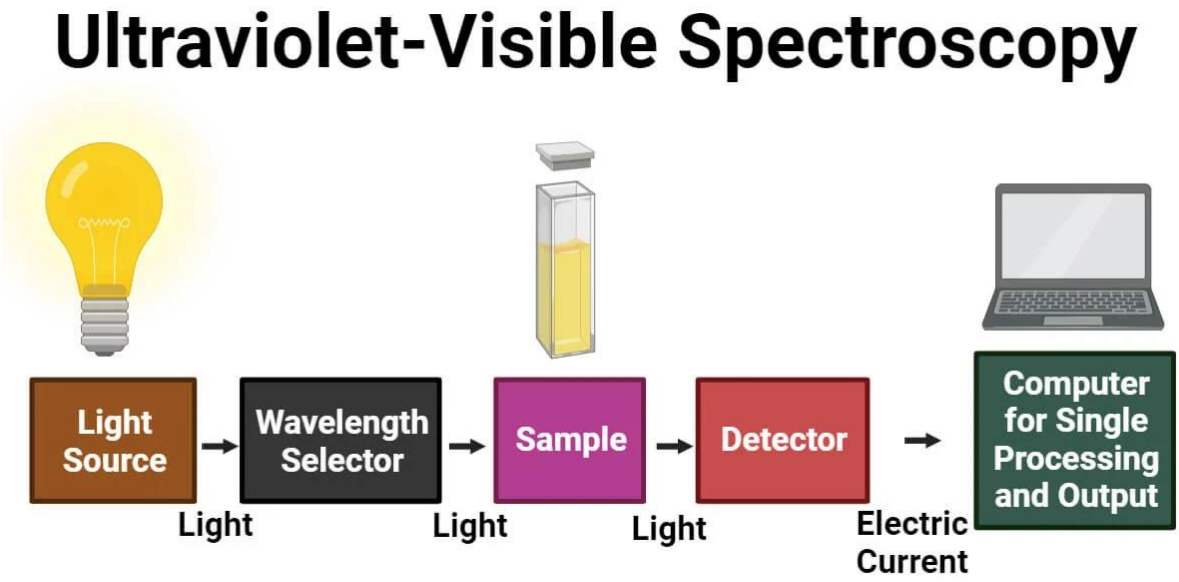


Fig. 1: UV–Visible Spectroscopy.

1.2 HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC):

High Performance Liquid Chromatography (HPLC) is a powerful separation technique used for qualitative and quantitative analysis of pharmaceutical compounds. It operates on the principle of differential partitioning of analytes between a stationary phase and a mobile phase under high pressure. Separation is achieved based on differences in polarity, molecular size, and interaction with the stationary phase.

HPLC offers high sensitivity, specificity, reproducibility, and accuracy, making it a preferred method for drug analysis in bulk and dosage forms. Reverse Phase HPLC (RP-HPLC), commonly employing C18 columns, is widely used due to its versatility and compatibility with a broad range of pharmaceutical compounds. Detection is generally carried out using UV or photodiode array detectors. HPLC methods are validated according to regulatory guidelines to ensure reliability in terms of linearity, precision, accuracy, limit of detection (LOD), and limit of quantification (LOQ).

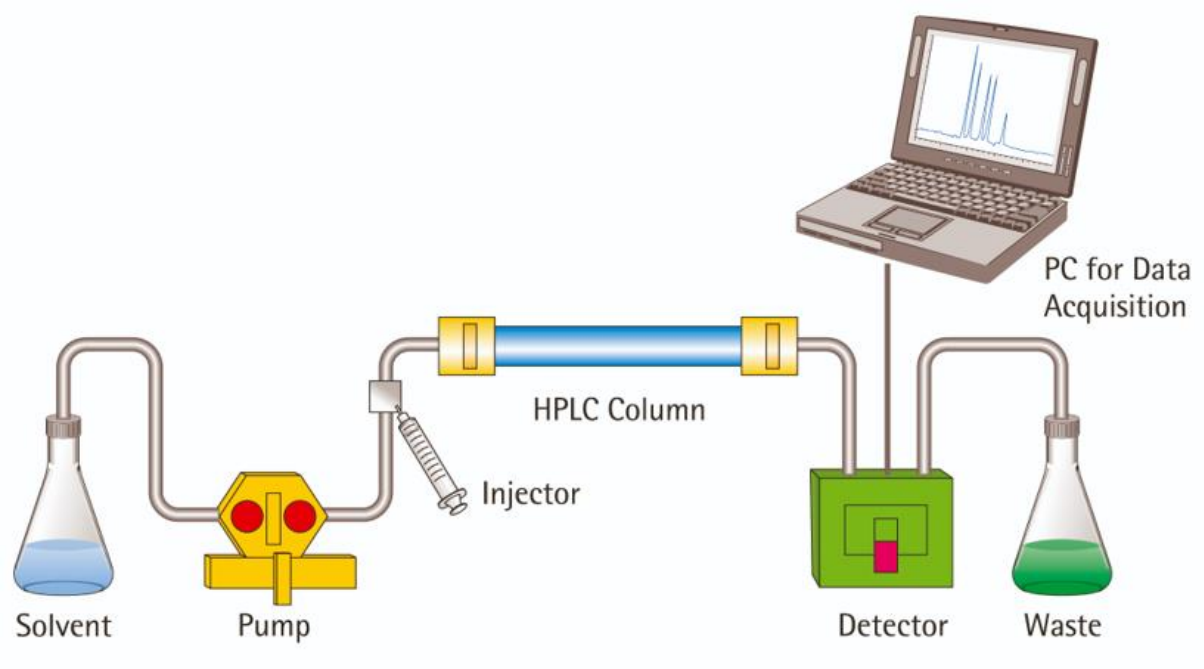


Fig. 2: High Performance Liquid Chromatography.

1.3 LIQUID CHROMATOGRAPHY–TANDEM MASS SPECTROMETRY (LC-MS/MS):

Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS) is an advanced analytical technique that combines the separation capability of liquid chromatography with the high sensitivity and selectivity of mass spectrometry. After chromatographic separation, analytes are ionized and detected based on their mass-to-charge (m/z) ratio.

LC-MS/MS provides superior sensitivity, allowing detection of drugs at nanogram or even picogram levels. It is especially valuable in bioanalytical studies, pharmacokinetic profiling, impurity analysis, and trace-level quantification. The use of tandem mass spectrometry (MS/MS) enhances specificity by monitoring specific precursor-to-product ion transitions, reducing interference from complex biological matrices.

Due to its accuracy, sensitivity, and robustness, LC-MS/MS has become an essential tool in modern pharmaceutical research and quality control, particularly for drugs requiring highly sensitive detection.

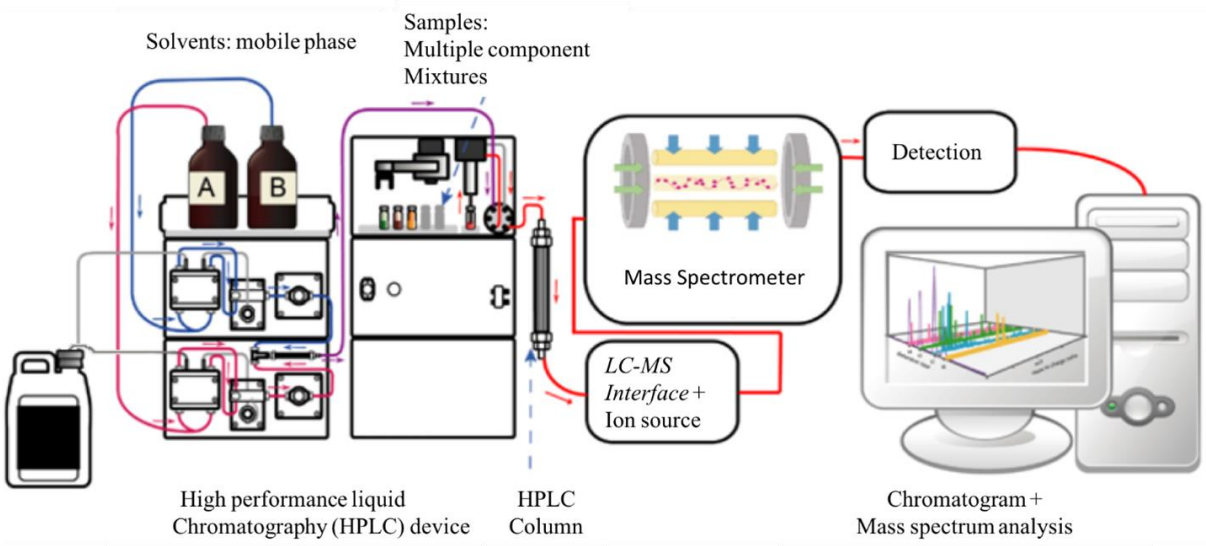


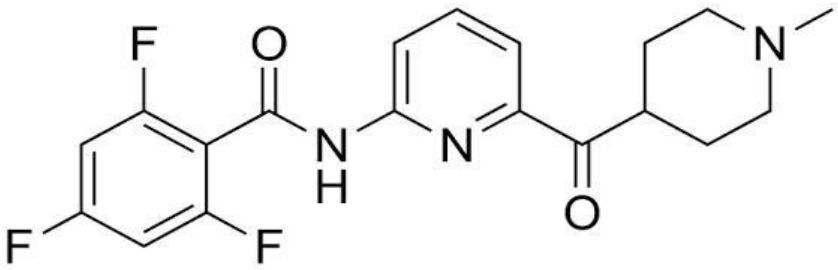
Fig. 3: Liquid Chromatography–Tandem Mass Spectrometry.

2. DRUG NAME: LASMIDITAN

2.1 PHYSIO-CHEMICAL PROPERTIES:

- ✓ **Chemical Class:** selective 5-HT1F (serotonin) receptor agonist
- ✓ **Chemical Name:** 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-pyridin-2-yl] benzamide.
- ✓ **Molecular Formula :** $C_{19}H_{18}F_3N_3O_2$
- ✓ **Molecular Weight :** 377.367g/mol.
- ✓ **Strength** : 50 mg
- ✓ **Salt Form:** Lasmiditan hemi succinate.
- ✓ **Appearance:** White round shaped film coated tablet.
- ✓ **Half Life** : 5 to 7 hours.
- ✓ **Solubility:** Lasmiditan is soluble in DMSO .sparingly soluble in water and N-butyl alcohol and slightly soluble in Ethanol & insoluble in acetone, acetic acid &ethyl acetate.

2.2 STRUCTURE



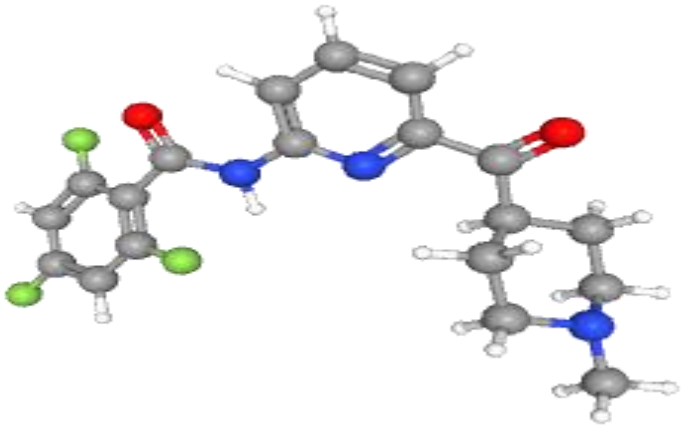


Fig. 4: Structure of Lasmiditan.

2.3 DESCRIPTION

- Lasmiditan is an orally active drug used for the acute treatment of migraine with or without aura. It is a selective 5-HT1F (serotonin) receptor agonist, belonging to the class called ditans.Unlike triptans, Lasmiditan does not cause vasoconstriction, making it safer for patients with cardiovascular risk
- It acts mainly on the central nervous system, reducing migraine pain by inhibiting trigeminal nerve pathways
- Common adverse effects include dizziness, fatigue, paresthesia, and sedation.
- Lasmiditan can be quantitatively estimated by UV–Visible spectroscopy, as it shows characteristic absorbance in the UV region due to its aromatic and heterocyclic functional groups.

2.4 MECHANISM OF ACTION:

Migraine attacks are initiated by the activation of trigeminal sensory neurons, which play a central role in the pathophysiology of migraine. During a migraine episode, increased neuronal activity within the trigeminovascular system leads to the release of pain-mediating neuropeptides and transmission of nociceptive signals to the central nervous system (CNS). Upon administration, lasmiditan selectively binds to 5-hydroxytryptamine 1F (5-HT_1F) receptors located predominantly in the CNS and on trigeminal neurons. Activation of these receptors results in suppression of trigeminal neuronal activity, thereby inhibiting the release of calcitonin gene-related peptide (CGRP) and other pro-inflammatory neuropeptides involved in migraine pathogenesis. This inhibition reduces central pain signal transmission within the trigeminovascular pathway. Consequently, lasmiditan provides effective relief

from migraine pain without causing vasoconstriction, as it does not significantly activate 5-HT_1B receptors associated with vascular constriction.

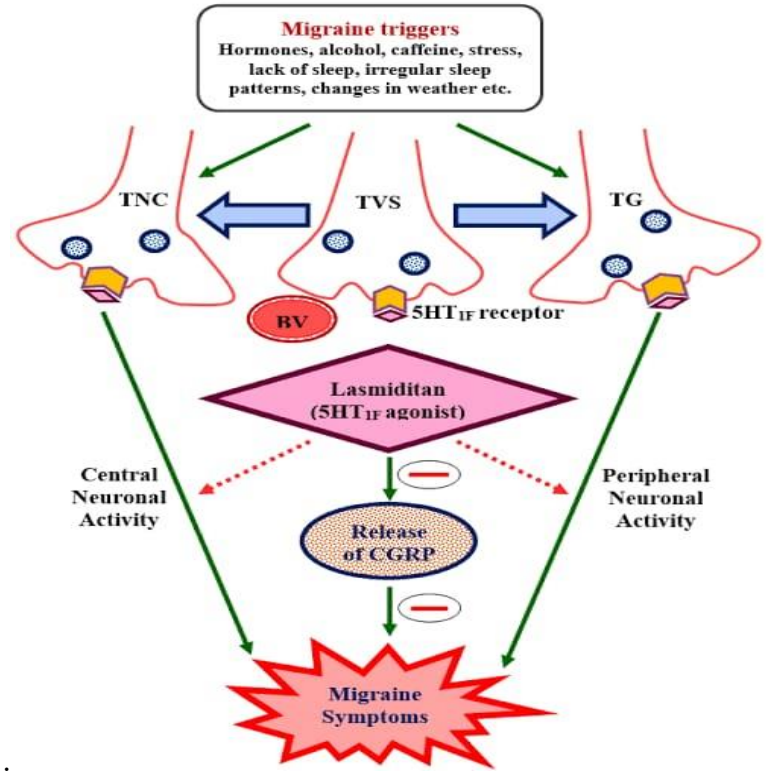


Fig. 5: Mechanism Action Of Lasmiditan.

2.5 USES

1. Acute treatment of migraine with aura.
2. Acute treatment of migraine without aura.
3. Relief of moderate to severe migraine attacks.
4. Reduction of migraine-associated symptoms (nausea, photophobia, phonophobia).
5. Suitable option for patients with cardiovascular risk where triptans are contraindicated.

2.6 ADVERSE EFFECT:

1. Dizziness, Fatigue, Nausea
2. Paresthesia (tingling sensation)
3. Somnolence (drowsiness)
4. Driving impairment (significant CNS depression; patients should avoid driving for at least 8 hours after dose)
5. Serotonin syndrome (especially when used with SSRIs/SNRIs)
6. Bradycardia (decreased heart rate)

7. Euphoria or mood changes
8. Hallucinations

2.7 PHARMACODYNAMICS:

Lasmiditan is a selective 5-hydroxytryptamine 1F (5-HT$_1$F) receptor agonist that exerts its therapeutic effect through central neuronal mechanisms. By binding to 5-HT$_1$F receptors located on trigeminal neurons in the central nervous system, it activates inhibitory G-protein–coupled pathways, leading to decreased cyclic AMP (cAMP) production and reduced neuronal excitability. This action suppresses the release of calcitonin gene-related peptide (CGRP) and other pain-mediating neuropeptides involved in migraine pathophysiology. Consequently, lasmiditan reduces trigeminal nociceptive transmission and provides effective relief from migraine without causing significant vasoconstriction, as it lacks activity at vascular 5-HT1B receptors.

2.8 PHARMACOKINETICS

Absorption: Lasmiditan is rapidly absorbed following oral administration, with peak plasma concentrations (Cmax) typically reached within approximately 1.5 to 2 hours. The drug demonstrates good oral bioavailability, and food may slightly delay the time to reach peak concentration but does not significantly affect overall systemic exposure.

Distribution: Lasmiditan exhibits moderate plasma protein binding (approximately 55–60%) and distributes widely throughout the body. Importantly, it readily crosses the blood–brain barrier, allowing effective penetration into the central nervous system, which is essential for its antimigraine action.

Metabolism: Lasmiditan is primarily metabolized in the liver through non–cytochrome P450 enzymatic pathways, mainly via ketone reduction and other non-CYP mediated processes. As a result, it has a relatively low potential for clinically significant CYP-related drug–drug interactions.

Excretion: The elimination half-life of lasmiditan is approximately 5 to 6 hours. It is excreted predominantly in the urine in the form of inactive metabolites, with a smaller portion eliminated via feces.

3. LITERATURE REVIEW

Table 1: UV Spectrophotometric Method

Stationary Phase/ Instrumentation	Mobile Phase/ Solvent	Flow Rate, Method Of Detection, Retention Time	Result	Reference
Stationary phase Not applicable **instrumentation** Shimadzu UV-1700 Pharmaspec model spectrophotometer	methanol	Flow rate not applicable, UV – visible absorbance at 626nm	The method obeys Beer-Lambert's law Linearity -10 to 50µg/mlR^2=0.9993 Precision=8.49% Percentage recovery=98.92% and is suitable for routine quantitative estimation of lasmiditan	Syed Imam Pasha (2024)

Table 2: High Performance Liquid Chromatography (HPLC).

Stationary Phase	Mobile Phase	Flow Rate, Method Of Detection Retention Time	Results	Reference
column of inertsil ODS (150x4.6mm, 3.5µm)	0.1% ortho phosphoric acid and Acetonitrile in 50:50	1ml/min UV 258 nm Retention time=3.203 min	Linearity =5 to 75 µg/ml with r^2=0.999 % assay =99.56 LOD=0.15 µg/ml LOQ=0.45µg/ml Robustness=97.595±0.041	Harshali Solanki (2022)

Table 3: Reverse phaseHigh Performance Liquid Chromatography (RP-HPLC).

Stationary Phase	Mobile Phase	Flow Rate Method Of Detection Retention Time	Results	Reference
C18 column (4.6 x 250 mm, particle size 5µm)	Methanol: water (75:25) V/V	Flow rate=1.0ml/min. detection wavelength was 271 nm. Rt=2.650 min	Linearity is 20 to 70µg/mL with corelation coefficient 0.999 LOD and LOQ is 0.0041 and 0.0126 Accuracy=99.93 to 100.34% %RSD=0.0041 and 0.0126 for both inter day and intra day precisions.	Vakkanti Venkata Sridevi (2022)

Table 4: Liquid Chromatography-Mass Spectrometry (LC-MS/MS).

Stationary Phase	Mobile Phase	Flow Rate, Instrumentation And Retention Time	Results	Reference
C18 column (SP) with dimensions of 150 mm, 4.6 mm i.d., and 3.5 µm	Acetonitrile: 0.1% formic acid (70:30)	1 mL/min, Tandem Quadrupole (Triple Quadrupole) MS detector, Rt =2.33 min.	Linearity is between 12.50 ng/mL and 75 ng/mL and regression coefficient is 0.999 LOD and LOQ is 0.66 ng/mL and 2.22 ng/mL %RSD =0.83 and 0.64 for both intra and inter day precision. Accuracy=100.52 %	D. Chinna Babu (2023)

4. CONCLUSION

Lasmiditan is a novel, centrally acting selective 5-HT$_1$F receptor agonist that provides effective acute relief from migraine without inducing vasoconstriction. Its unique mechanism of action, favorable pharmacokinetic profile, and suitability for patients with cardiovascular risk make it a significant advancement in migraine therapy.

Validated analytical techniques such as UV spectroscopy, HPLC, RP-HPLC, and LC-MS/MS ensure accurate and precise quantitative estimation of lasmiditan in pharmaceutical formulations. Overall, lasmiditan represents an important therapeutic option in modern migraine management, combining efficacy, safety, and reliable analytical characterization.

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