1.4 Drug profile

1.4.1 Rufinamide

1.4.1.1 Description\textsuperscript{15-16}:

Rufinamide is approved by USFDA in November 2008, indicated for adjunctive treatment of seizures associated with Lennox- Gastaut syndrome in children 4 years and older and adults

![Chemical Structure of Rufinamide](imageURL)

**Structure:**

**Chemical Name:** 1-(2, 6- Difluorobenzyl)-1H-1, 2, 3-triazole-4-carboxamide\textsuperscript{15}

**Generic Names:** Rufinamide (OS: USAN, BAN), CGP-33101 (IS: Novartis), RUF 331(IS: Novrtis)

**Brand Names:** Banzel, Invelon

**Empirical Formula:** \( \text{C}_{10}\text{H}_8\text{F}_2\text{N}_4\text{O} \)

**Relative molecular mass:** 238.19

**CAS Registry Number:** 106308-44-5

**Percent composition:** C 50.42\%, H 3.39\%, F 15.95\%, N 23.52\%, O 6.72\%

**Therapeutic category:** use in treatment of lennox gastaut syndrome, use as antiepileptic agent

**Appearance, color & taste:** A white, crystalline, powder, odorless, bitter tasting
1.4.1.2 Physicochemical property\textsuperscript{17-21}

**Solubility:** Practically insoluble in water, slightly soluble in THF and methanol, very slightly soluble in ethanol and acetonitrile, soluble in DMSO

**Melting point:** 237- 240°C

**Storage:** stored at 15-30°C

**U.V spectrum:** $\lambda_{\text{max}}$ 218 nm

1.3.1.3 Pharmacokinetics\textsuperscript{22-26}

**Absorption:** Rufinamide is well absorbed after oral administration. However, the bioavailability is decrease as dose increase. $T_{\text{max}}$ is between 4 and 6 hour. Food increase the absorption extent 34%.

**Distribution:** Rufinamide is 30% bound to plasma proteins. Distribution appears even between erythrocytes and plasma with an apparent volume of distribution of 50 L. The apparent volume of distribution is increase with increasing body surface area and in larger in adolescent.

**Protein binding:** protein binding capacity is low i.e. approximately 34%

**Metabolism:** It is extensively metabolized to pharmacologically inactive metabolites – carboxylic acid derivative, primarily by carboxyl esterase mediate hydrolysis. This metabolite is easily excreted in the urine. Rufinamide is weak inhibitor of CYP2E1 and weak inducer of CYP3A4.

**Elimination:** Elimination half-life is 6 to 10 h. Renal elimination accounts for 85% of an administered dose, with less than 2% recovered unchanged.

1.4.1.4 Pharmacology:

Rufinamide is indicated as an adjunctive therapy in the treatment of seizures associated with lennox gastaut treatment. It is triazole derivative structurally unrelated to any other
antiepileptic drug. Rufinamide is believed to prolong the refractory period of the voltage
dependent sodium channels, making neurons less likely to fire.

**Mechanism of Action:** Principle mechanism of action of Rufinamide is modulation of
the activity of sodium channels and, in particular, prolongation of the inactive state of the
channel. Rufinamide significantly slowed sodium channel recovery from inactivation
after a prolonged prepulse in cultured cortical neurons, and limited sustained repetitive
firing of sodium–dependent action potentials. (EC50 of 3.8 μM)\(^{27-29}\)

**Indication & clinical use:** Rufinamide is indicated for LGS or other treatment resistant
generalized epilepsy patient.

**Contraindication:** Rufinamide is contraindicated in patients with familial short QT
syndrome\(^{30}\)

**Adverse reaction:** adverse effect seen during clinical trials includes somnolence,
dizziness, headache, ataxia, nausea, vomiting and fatigue. Rufinamide has been shown
the shorten QT interval and so it is contraindicated in patients with familial shorten QT
interval. Some dermatological side effects like rash, pruritis also seen with Rufinamide.
Sudden withdrawal of Rufinamide may precipitate seizure.\(^{31-36}\)

**Drug interaction:** Interactions with other medicine\(^{37-40}\)

**Barbiturates (eg. phenobarbital), hydantoins (eg. phenytoin):** Plasma concentrations
may be increased by Rufinamide, while Rufinamide plasma concentrations may be
decreased, especially in children.

**Carbamazepine:** Carbamazepine and Rufinamide plasma concentrations may be
decreased.

**Hormonal contraceptives:** Co-administration of Rufinamide 800mg b.i.d. and a
combined oral contraceptive (ethinyloestradiol 35μg and norethindrone 1mg) for 14 days
resulted in a mean decrease in the ethinyl estradiol AUC\(_{0-24}\) of 22% and in norethindrone
AUC\(_{0-24}\) of 14%. Efficacy of hormonal contraceptives may be decreased; additional
nonhormonal forms of contraception are recommended when using Rufinamide.
Lamotrigine: Plasma concentrations may be decreased by Rufinamide, especially in children.

Primidone: Rufinamide plasma concentrations may be decreased, especially in children.

Triazolam: Plasma concentrations may be decreased.

Valproic acid: Rufinamide plasma concentrations may be elevated, increasing the pharmacologic effects and adverse reactions. Patients stabilized on Rufinamide before starting valproate should begin valproate at a low dosage and titrate to a clinically effective dose. Similarly, patients on valproate should begin at a Rufinamide dosage lower than 10 mg/kg/day (children) or 400 mg/day (adults). Effects are greater in children. In children valproate administration may lead to elevated level of Rufinamide upto 70%

Precautions\textsuperscript{41-42}: Antiepileptic drugs (AEDs), including Rufinamide, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

Dosage & administration\textsuperscript{43}: 

Available dosage form: 100mg, 200mg & 400mg film coated Tablet

Children four years and older with LGS: Treatment should be initiated at a daily dose of approximately 10 mg/kg/day administered in two equally divided doses. The dose should be increased by approximately 10 mg/kg increments every other day to a target dose of 45 mg/kg/day or 3200 mg/day, whichever is less, administered in two equally divided doses.

Adults with LGS: Treatment should be initiated at a daily dose of 400-800 mg/day administered in two equally divided doses. The dose should be increased by 400-800 mg
every other day until a maximum dose of 3200 mg/day, administered in two equally divided doses is reached.

**Storage:**

Film coated tablet: Do not store above 30°C.

Oral suspension: This medicinal product does not require any special storage conditions.
1.4.2 Lacosamide:

1.4.2.1 Description\textsuperscript{44-45}:

Lacosamide is approved by the USFDA in October 2008 for the adjunctive treatment of the partial onset of seizures. Lacosamide has only one chiral center & is administered in the R form.

\begin{center}
\includegraphics[width=0.5\textwidth]{Structure.png}
\end{center}

\textbf{Structure:}

\textbf{Chemical Name:} 2-acetamido-N-benzyl-3methoxypropionamide

\textbf{Generic Names:} Lacosamide, Erlosamide

\textbf{Brand Names:} Vimpat

\textbf{Empirical Formula:} C\textsubscript{13}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}

\textbf{Relative molecular mass:} 250.29 gm/mol

\textbf{CAS Registry Number:} 175481-36-4

\textbf{Percent composition:} C 62.38\%, H 7.25\%, N 11.19\%, O 19.18\%

\textbf{Therapeutic category:} use in treatment of partial onset of seizure

\textbf{Appearance, color & taste:} A white to light yellow non hygroscopic powder, bitter in taste
1.4.2.2 Physicochemical property\textsuperscript{46-49}

**Solubility:** Sparingly soluble in water, slightly soluble in acetonitrile and ethanol

**Melting range:** 140-146° C

**Boiling Point:** 536.447°C at 760 mmHg

**Storage and stability:** store at 15-30°C

**U.V spectrum:** $\lambda_{\text{max}}$ 210 nm

1.3.2.3 Pharmacokinetics\textsuperscript{50-51}

**Absorption:** Lacosamide is a modified amino acid with fast and complete absorption. The bioavailability after oral administration approaches 100%. The maximum Lacosamide plasma concentration about 1-4 hour after oral administration and the pharmacokinetic of Lacosamide are dose proportional. Food does not affect the absorption of Lacosamide.

**Distribution:** Volume of distribution of Lacosamide is approximately 0.6 L/Kg. Its protein binding capacity is about less than 15%.

**Metabolism:** 95% of the dose is excreted in the urine as drug and metabolites. The metabolism of Lacosamide has not been completely characterized. The major compounds excreted in urine are unchanged Lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%. A polar fraction proposed to be serine derivatives accounted for approximately 20% in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of additional metabolites were found in the urine. In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed in vivo. The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.
**Elimination:** Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces mainly as unchanged drug (40%), 30% as the o-desmethyl metabolite and approximately 20% as a structurally unknown inactive polar metabolites. The elimination half-life of the unchanged drug is approximately 13 hours. The pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.

**1.4.2.4 Pharmacology:**

Lacosamide is indicated for the adjunctive treatment of partial onset seizures in patients with ≥ 17 years with epilepsy. Lacosamide is available in two different enantiomers i.e. R & S form. Amongst these (R) form is pharmacologically more potent.

**Mechanism of Action**: The mechanism of action of Lacosamide, (R)-2-acetamido-N-benzyl-3-methoxypropionamide, has not been fully defined. It is a functionalized amino acid that selectively enhances slow inactivation of voltage-gated sodium channels (VGSCs), increasing the proportion of sodium channels unavailable for depolarization. This produces stabilization of neuronal membranes and inhibition of sustained repetitive neuronal firing. Unlike other antiepileptics, including carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, and topiramate, lacosamide does not alter fast inactivation of VGSCs. Lacosamide also interacts with collapsin-response mediator protein 2 (CRMP-2). This protein is part of a signal transduction cascade of neurotrophic factors involved in neuronal differentiation, regulation of gene expression, polarization, and axonal outgrowth. It has been proposed that binding at CRMP-2 may produce a neuroprotective effect, reducing glutamate-induced excitotoxicity and enhancing the clinical efficacy of Lacosamide.
Indication & clinical use: Lacosamide is indicated for partial onset of seizures in adult patients with epilepsy.

Contraindication: Lacosamide is contraindicated when hypersensitivity reaction persist.

Adverse reaction: 

CNS: Dizziness (53%), ataxia, fatigue (15%), headache (14%), tremor (12%), somnolence (8%), balance disorder, memory impairment (6%), vertigo (5%), asthenia, gait disturbance (4%), depression (2%), bradycardia (post marketing).

Dermatologic: Contusion (4%), pruritis, skin laceration (3%).

EENT: Blurred vision, diplopia (16%); nystagmus (10%).

GI: Nausea (17%), vomiting (16%), diarrhea (5%).

Local: Injection-site pain or discomfort (3%), irritation (1%).

Drug interaction: Interactions with other medicine:

No clinically significant drug interactions with Lacosamide have been identified. A small (20%) increase in ethinyl estradiol has been reported in women taking Lacosamide with oral contraceptives. Minor reductions in serum concentrations (< 20%) occur in carbamazepine, phenytoin, and phenobarbital when given with lacosamide.

Precautions: Antiepileptic drugs (AEDs), including Lacosamide, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

In patients with known conduction problems or severe cardiac disease, obtain ECG before starting treatment and after titrating to steady state. Monitor patients for emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Closely monitor patients with coexisting hepatic and renal
impairment during dose titration.

Lacosamide is not recommended in patients with severe hepatic impairment. Ataxia and dizziness may occur with Lacosamide. So, advise patients not to drive or operate complex machinery until they are familiar with the drug's effects on their ability to perform. Atrial fibrillation and atrial flutter has been reported in patients with diabetic neuropathy who received treatment with Lacosamide.

Dose-related PR interval prolongation may occur. Use with caution in patients with known conduction problems (e.g., marked first-degree AV block, second-degree or higher AV block, sick sinus syndrome without a pacemaker) or with severe cardiac disease (e.g. myocardial ischemia, heart failure). Syncope has been reported in patients with diabetic neuropathy who were treated with Lacosamide.

**Dosage & administration**

**Available dosage form:** 50 mg, 100 mg, 150 mg & 200 mg film coated Tablet
10 mg/ml oral solution
10 mg/ml injection

**Partial-Onset Seizures**

**Adults and Children 17 y of age and older**

PO/IV Start with 50 mg twice daily. The dosage may be increased by 50 mg twice daily at weekly intervals up to the recommended maintenance dosage of 200 to 400 mg/day, based on response and tolerability.

**Hepatic Function Impairment**

**Adults and Children 17 y of age and older**

PO/IV Titrate the dose with caution. Max dosage of 300 mg/day is recommended in patients with mild or moderate hepatic impairment. Not recommended in patients with severe hepatic impairment.

**Renal Function Impairment**

**Adults and Children 17 y of age and older mild or moderate renal function impairment**

PO/IV No dosage adjustment is needed.
Severe renal function impairment (CrCl less than 30 mL/min) and ESRD

PO/IV Max dosage is 300 mg/day. Following a 4-hour hemodialysis treatment, consider supplementation with up to 50% of the dose.

**Storage:**

Tablets: This medicinal product does not require any special storage conditions.

Syrup: Do not refrigerate.

Solution for infusion: Do not store above 25°C.
1.5 Preliminary identification of drug substances (API)

1.5.1 Melting point: Melting point of the procured drug substances were recorded using Veego melting point apparatus and were uncorrected and listed in table 1.1

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Drug (A.P.I)</th>
<th>Reported melting point (˚C)</th>
<th>Observed melting point (˚C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rufinamide</td>
<td>237-240&lt;sup&gt;[19]&lt;/sup&gt;</td>
<td>235-238</td>
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<tr>
<td>2</td>
<td>Lacosamide</td>
<td>140-146&lt;sup&gt;[45]&lt;/sup&gt;</td>
<td>138-144</td>
</tr>
</tbody>
</table>

1.5.2 TLC Analysis: TLC analysis in three different mobile phases for each drug were tried in order to check the purity of the compounds. No other spot/spots were detected, confirming the high purity of the samples.

1.5.3 UV Spectral data: UV spectrum of both the APIs were recorded using Shimadzu UV-1700 instrument using methanol as solvent and are reported in table 1.2

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Drug (A.P.I)</th>
<th>Reported UV λ&lt;sub&gt;max&lt;/sub&gt; (nm)</th>
<th>Observed UV λ&lt;sub&gt;max&lt;/sub&gt; (nm)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Rufinamide</td>
<td>218&lt;sup&gt;[19]&lt;/sup&gt;</td>
<td>218</td>
</tr>
<tr>
<td>2</td>
<td>Lacosamide</td>
<td>210&lt;sup&gt;[45]&lt;/sup&gt;</td>
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</tbody>
</table>
1.5.4 IR spectral data

![Figure 1.1: IR spectrum of Rufinamide](image)

**Table 1.4 IR spectral interpretation for Rufinamide**

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Reported wave number (cm(^{-1}))</th>
<th>Observed wave number (cm(^{-1}))</th>
<th>Functional Group</th>
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</thead>
<tbody>
<tr>
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<td>-NH(_2)</td>
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<tr>
<td>2</td>
<td>1634</td>
<td>1629.3</td>
<td>C=O</td>
</tr>
<tr>
<td>3</td>
<td>716-1275</td>
<td>889-1037</td>
<td>C-F stretch</td>
</tr>
<tr>
<td>4</td>
<td>1060</td>
<td>1037</td>
<td>C-N Stretch</td>
</tr>
</tbody>
</table>
Figure 1.2: IR spectrum of Lacosamide

Table 1.5 IR spectral interpretation for Lacosamide

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Reported wave number (cm(^{-1}))</th>
<th>Observed wave number (cm(^{-1}))</th>
<th>Functional Group</th>
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<td>1082</td>
<td>C-N stretch</td>
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