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A COMPREHENSIVE REVIEW ON ANALYTICAL VALIDATION METHODS OF CENOBAMATE AND UPADACITINIB

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Abstract

A new antiepileptic medication called cenobamate was just licenced to treat adult partial-onset seizures. By specifically focusing on the persistent sodium current, its special method of action lowers neuronal excitability and the spread of seizures. Cenobamate has been shown to be safe and effective in clinical trials, resulting in notable decreases in the frequency of seizures and enhancements in the patient's quality of life. Patients with uncontrollably occurring seizures may find it to be a desirable option due to its excellent pharmacokinetic profile and few medication interactions. This study examines the possible advantages and disadvantages of cenobamate use in the treatment of epilepsy and summarises the available data in favour of it. A Janus kinase (JAK) inhibitor called The medication upadacitinib is authorised Regarding the management ofmoderate-to-severe adult inflammatory arthritis (RA). Upadacitinib reduces inflammation and joint injury by inhibiting pro-inflammatory cytokine signalling by blocking JAK enzymes.Its side effects are tolerable and its safety profile is typically acceptable. This review looks at the data that is currently available to support the use of Upadacitinib in the therapy of RA, emphasising its safety, effectiveness, and potential as a treatment alternative for patients who don't respond well to traditional medications.

***Keywords*:** Antiepileptic, Cenobamate, Upadacitinib, Analytical methods.

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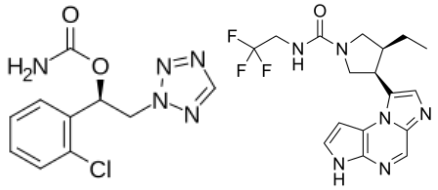
Introduction

The chemical formula for cenobamate, which is FDA-approved for treating focal seizers, is 1-(2-chlorophenyl)-1R)-1-(2H-1,2,3,4-tetrazol 2)-2y1) ethyl carbomate (figure 1a). Cenobamate is an oral antiseizure medicine that was licenced for medical use in the United States inNovember 2019 and placed under schedule V of the controlled substance act in March 2020. It is now being evaluated for the treatment of individuals with primary generalised tonic-clonic epileptic disorders. It is a brand-new, experimental medication that has attracted a lot of interest recently due to its revolutionary potential to treat neurological conditions like epilepsy. Cinabamate increases the activity of the neurotransmitter GABA, a crucial regulator of neuronal excitability, as a positive allosteric modulator of the GABA receptor [1]. An oral, second-generation selective janu kinase [JAK] inhibitor called Upadacitinib (figure 1b) [RINVOQ] is used to treat atopic dermatitis, or eczema. It is [2S,3R]-3-[aminomethyl]-2-ethylbutanoic acid chemically. It inhibits the immunological response by targeting the JAK1 enzyme. In January 2022, the US Food and Drug Administration (FDA) authorised Upadacitinib for the management of moderate to severe atopic dermatitis. Upadacitinib was given FDA approval in 2019 to treat moderate-to-severe rheumatoid arthritis (RA). In clinical trials, the medication showed strong efficacy and an acceptable safety profile. Its mode of action is the suppression of the JAK-STAT signalling system, which is important for controlling inflammation and immune cell activity [2].



(a) (b)

Figure 1: chemical structure of Cinobamate and Upadacitinib

Table 1: Physicochemical characteristics [3]:

S No.	Physicochemical parameters	Cinobamate	Upadacitinib
1	Liquability	soluble in water	Soluble in solvents that are organic, like DMSO and dimethyl formamide
2	P ka	14.28(strongest acidic) 1,7(strongest base)	4.11
3	Melting point	96.8-98.3°c	16-19oC
4	Boiling point	520.8+-60.0°c at 760mmhg	189o c
5	Density	1.6 +or-0.1g/cm3	1.6±0.1 g/cm3
6	Storage temperature	between 68°Fto 77°F or below 86°F,30°F	2-25oc
7	Form	Solid	solid
8	Colour	White	White
9	Half life	50 to 60 hrs	8-10 hrs
10	Dose	12.5 mg orally once a day for 1 – 2 weeks	15 mg once daily, 45mg once daily for 8 weeks

Mechanism of action of Cenobamate

One voltage-gated sodium channel blocker is cenobamate. It is a preferential inhibitor of persistent sodium current that selectively blocks the inactivated state of VGSCS. Cenobamate may also increase the presynaptic release of GABA (gamma-aminobutyric acid), which increases inhibitory GABAergic neurotransmission [4].

Mechanism of action of Upadacitinib

It's a tiny, oral chemical that blocks pro-inflammatory cytokines' use of the JAK-STAT signalling pathway. The general biological processes of immune system regulation, cell proliferation, and hemopoiesis are also facilitated by these same cytokines. The involvement of pro-inflammatory cytokines in inflammation plays a role in the JAK-STAT pathway's involvement in the pathogenesis of ulcerative colitis [5].

Table 2: Pharmacokinetic characteristics [6]:

S No.	pharmacokinetics	Cenobamate	Upadacitinib
1	Absorption	Oral	Oral
2	Distribution	Distributed into blood plasma	attaches itself to plasma proteins and distribute to bodily liquids
3	Metabolism	Glucuronidation	Metabolism is mediated by CYP3A4 with a potential minor contribution from CYP2D6
4	Excretion	Through urine	Through unchanged form of faeces[38%]and urine [24%].

Side Effects Of cinobamate

Drowsiness, dizziness, nausea, constipation, vomiting,diaherea, blurred vision, double vision[7].

Side Effects of Upadacotinib

Body aches or pain, Ear congestion, Headache, Loss of voice, Sneezing, Stuffy nose, Sore throat, Itching, pain, redness, swelling, Tenderness, Warmth on the skin [7].

Table 3: available marketed formulations of Cenobamate[8]:

S no.	Name	Dosage form	Dose available	Route of administration	Manufacturer
1	Ontozry	Tablet, film coated	200mg	Oral	Angelini pharma S.P.A, Aprilia, Italy
2	Ontozry	Tablet, film coated	150mg	Oral	Angelini pharma S.P.A, Aprilia, Italy
3	Ontozry	Tablet, film coated	100 mg	Oral	Angelini pharma S.P.A, Aprilia, Italy
4	Ontozry	Tablet, film coated	50 mg	Oral	Angelini pharma

					S.P.A, Aprilia, Italy
5	Ontozry		25+12.5 mg	Oral	Angelini pharma S.P.A, Aprilia, Italy

Table 4: available marketed formulation of Upadacitinib[9]:

S no.	Name	Dosage form	Dose available	Route of administration	Manufacturer
1	Rinvoq	Tablet, extended release.	15 mg	oral	Abbvie Inc
2	Rinvoq	Tablet, extended release.	30mg	oral	Abbvie Deutschland Gmb H and co.kg
3	Rinvoq	Tablet, extended release.	15 mg	oral	Abbvie Inc
4	Rinvoq	Tablet, extended release.	15 mg	oral	Abbvie Deutschland Gmb H and co.kg
5	Rinvoq	Tablet, extended release.	30 mg	oral	Abbvie Deutschland Gmb H and co.kg

Table no 5: HPLC, RP-HPLC, RP-UPLC, LC-MS/MS of cenobamate:

S no.	Method	Column	Mobile phase	Flowrate (ml/min)	Linearity (µg/ml)	Wave length (nm)	Retention time (min)	LOD (µg/ml)	LOQ (µg/ml)	Reference
1	HPLC	C18 (150mm×4.6mm;5µm)	50:50 (%v/v) of methanol and water	1.0	4.0-200.0	210	3.2	0.627	1.901	[10]
2	RP-HPLC	C18(150mm×4.6mm;5µm)	Acetonitrile and NKH2PO4(55:45)	1.0	2	272	2.908	0.01	0.03	[11]
3	RP-UPLC	C18(150mm×4.6mm;2.7µm)	Water: acetonitrile (50:50v/v)	0.3	12.5-75	271.0	1.012	0.05	0.16	[12]
4	LC-MS/MS	C18(150mm×4.6mm;5µm)	0.1% formic acid in 20:80%v/v ratio acetonitrile	0.6			1.65±0.05 min and 0.58 ±0.05 min		10	[13]
5	LC-MS/MS	C18	Ammonium formats and acetonitrile (50:50 v/v)		10-5000		1.27 and 0.96			[14]

Table no 6: HPLC-MS/MS, UPLC, UPLC-MS/MS, LC-MS/MS of Upadacitinib:

S no.	Method	Column	Mobile phase	Flowrate (ml/min)	Linearity (µg/ml)	Wave length (nm)	Retention time (min)	LOD (µg/ml)	LOQ (µg/ml)	Reference
1	HPLC-MS/MS	C18(2.1mm×150mm; 2.5µm)	Formic acid and aceto notrile				4.09	0.05	0.5 and 200	[15]

2	UPLC	C18(50mm×2.1mm ;1.7µm)	Aceto nitrile: methanol:0.1% tri fluro acetic acid(50:20:30v/v)	0.2	15.0-180.0	231.2	2,289	4.50	15.00	[16]
3	UPLC-MS/MS	C18(2.1mm×50mm ;1.7µm)	Acetonitrile and 0.1% formic acid in water	0.40	1-500				1	[17]
4	LC-MS/MS	C18(150mm×4.6mm; 4.5µm)	Acetonitrile: water (50:50)	1	12.2-100	283	3.12		10	[18]
5	LC-MS/MS	C18(4.6mm×150mm ;5µm)	0.1%formic acid: acetonitrile (20:80%v/v)	0.6	10.0-500.0		1.65±0.05	1.03	0.34	[19]

Conclusion

The several analytical techniques reported for the determination of Cenobamate and Upadacitinib are summarised in the current review. To determine the levels of Cenobamate and Upadacitinib, the analytical techniques HPLC, HPLC-MS/MS, RP-HPLC, UPL, RP-UPLC, UPLC-MS/MS, and LC-MS/MS were used. The reports indicate that analytical approaches are recommended. Upadacitinib and Cenobamate estimation is the main application of LC-MS/MS.

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