Cyclobenzaprine HCL Sublingual Tablets (TONMYA) in Fibromyalgia
National Drug Mini-Monograph
May 2026
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA PRESCRIBING INFORMATION[1]

Description / MOA	Cyclobenzaprine HCl sublingual (SL) is structurally related to tricyclic antidepressants (TCAs). The mechanism of action of cyclobenzaprine for the treatment of fibromyalgia in adults is unknown. In *in vitro* pharmacology studies, cyclobenzaprine demonstrated functional antagonism of M1-muscarinic acetylcholine, H1-histaminergic, α1-adrenergic, and 5-HT2A receptors.
Indication Under Review	Treatment of fibromyalgia in adults.
Dosage Regimen	The dosage of cyclobenzaprine HCl SL begins with a starting dose of 2.8 mg (1 SL tablet) once daily at bedtime for the first 14 days. The target dose is 5.6 mg (2 SL tablets) once daily at bedtime starting on Day 15. The maximum recommended dosage is 5.6 mg once daily. In geriatric patients, the maximum recommended dosage is 2.8 mg administered SL once daily at bedtime. For patients with mild hepatic impairment (Child Pugh A), the recommended dosage is 2.8 mg administered SL once daily at bedtime. Use is not recommended in patients with moderate or severe hepatic impairment.
Dosage Forms Under Review	Sublingual tablets: 2.8mg cyclobenzaprine HCl

EFFICACY CONSIDERATIONS

Trial	**Lederman, et al. RESILIENT trial[2]**
Design	A randomized, double-blind, placebo-controlled, phase 3 clinical trial conducted at 33 U.S sites.
Population	N = 456 (modified intent-to-treat). Adults 18-65 years old (mean age 49.4 years) with a primary diagnosis of fibromyalgia (based on 2016 revisions of the 2010/11 Fibromyalgia Diagnostic Criteria). Patients were required to have a 7-day baseline Numeric Rating Scale (NRS) average daily pain intensity score ≥4 and ≤9. Overall, **95.4%** of patients were female. Mean FM duration ~ 9 years.
Intervention	Patients were randomized 1:1: cyclobenzaprine HCl SL (TNX-102 SL) 2.8mg nightly for 2 weeks, then 5.6 mg nightly for 12 weeks (n = 231) to matching placebo tablets (n = 225).
Results	TNX-102 SL demonstrated significant Improvement in the prespecified primary endpoint and all six key secondary endpoints versus placebo.

Primary Outcome	Cyclobenzaprine (TNX-102) SL	Placebo	Treatment Difference	P value
Change in weekly average of daily diary NRS pain intensity scores	–1.8 (n=231)	–1.2 (n=225)	-0.7	< 0.001

Secondary Endpoints: All six prespecified key secondary endpoints showed statistically significant improvement with TNX-102 SL versus placebo (p<0.001) including Patient Global Impression of Change (PGIC), Fibromyalgia Impact Questionnaire – Revised (FIQ-R)symptoms and function domains and fatigue and sleep-related measures.

58.9% of patients in the TNX-102 SL group experienced a treatment-emergent adverse event (TEAE) vs. 36.7% in the placebo group. Most common were local oral effects: oral hypoesthesia, product taste abnormal and oral paresthesia. The most common systemic TEAEs were COVID-19, headache and somnolence. Discontinuation rates: 6.1% TNX-102 SL vs 3.5% placebo. No deaths reported.

Trial	**Lederman et al. RELIEF trial[3]**
Design	A randomized, double-blind, placebo-controlled, multicenter Phase 3 clinical trial.
Population	N = 503 (intent to treat). Adults 18-65 years (mean age 49.6) meeting 2016 ACR fibromyalgia diagnostic criteria. Patients required to have 7-day average daily pain 4-9. Mean age 49.6 years; 95% female. Mean FM duration ~9.1 years.
Intervention	Patients were randomized 1:1: cyclobenzaprine HCl SL (TNX-102 SL) 2.8mg nightly for 2 weeks, followed 5.6 mg nightly for 12 weeks (n = 248) to matching placebo tablets (n = 255).
Results	TNX-102 SL demonstrated significant improvement in the primary endpoint vs placebo. Although the first key secondary endpoint (PGIC) did not meet the prespecified threshold for statistical significance, all other secondary endpoints showed significant improvements across symptoms, function, sleep and fatigue.

Primary Outcome	Cyclobenzaprine (TNX-102) SL	Placebo	Treatment Difference	P value
Change in weekly average of daily diary NRS pain intensity scores	–1.91 (n=248)	–1.51 (n=225)	-0.4	0.01

Responder Analysis: 46.8% of TNX-102 SL-treated patients achieved ≥ 30% reduction in daily pain vs 34.9% of placebo (p = 0.006)

59.7% of patients in the TNX-102 SL group experience TEAE vs 46.3% in the placebo group. Most common were local oral effects: oral hypoesthesia, oral paresthesia and product taste abnormal. The most common systemic TEAE were fatigue and sedation that typically mild and transient (< 60 mins) and temporarily associated with dosing. Discontinuation rates: 8.9% TNX-102 SL vs 3.9% placebo. No deaths reported.

SAFETY CONSIDERATIONS[1]	
Boxed Warnings	None
Contraindications	Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation. During the acute recovery phase of MI, and in patients with arrhythmias, heart block or conduction disturbances, or CHF. Hyperthyroidism
Other Warnings	Embryofetal toxicity, serotonin syndrome; TCA like ADRs (e.g. cardiac reactions and may lower seizure threshold); atropine like ADRs; oral mucosal ADRs; CNS depression
AEs in ≥ 5% of patients	Oral hypoesthesia, oral discomfort, abnormal product taste, oral paresthesia, somnolence, oral pain
Drug Interactions	MAO inhibitors (life threatening), alcohol/barbiturates and other CNS depressants (enhance CNS depressant effects), tramadol (increase seizure risk), guanethidine (block antihypertensive effects), serotonergic drugs (may result in serotonin syndrome)
Pregnancy	May cause neural tube defects when administered 2 weeks prior to conception and through the first trimester of pregnancy; effective contraception is advised for females of reproductive potential during treatment and for 2 weeks after the final dose. Verify pregnancy status prior to treatment (in patients who can become pregnant).
Lactation	No data available
Administration	Administer after completion of evening oral care (eg, brushing teeth); drink a few sips of water prior to administration to moisten mouth, then place tablet under the tongue and allow to dissolve completely. Do not cut, chew, crush, or swallow whole. Do not talk for ≥5 minutes after administration; avoid eating or drinking for at least 15 minutes after tablet has completely dissolved and preferably avoid any hot, cold, or acidic beverages preferably until morning.

THERAPEUTIC ALTERNATIVES

Drug	VANF	CFU	FDA Indication	Guidelines: EULAR Recommendations [5]
Cyclobenzaprine HCl Sublingual (TONMYA)	Pending Review		Treatment of fibromyalgia in adults	
Duloxetine (CYMBALTA)	Formulary	No	Management of fibromyalgia in adult and pediatric patients ≥ 13 years of age	Level of evidence: 1a, Grade A, Weak for (100% agreement)
Pregabalin (LYRICA)	Formulary	No	Management of fibromyalgia (IR only)	Level of evidence: 1a, Grade A, Weak for (94% agreement)
Milnacipran (SAVELLA)	Non-Formulary	No	Management of fibromyalgia	Level of evidence: 1a, Grade A, Weak for (100% agreement)
Amitriptyline (ELAVIL)	Formulary	No	Off-label for fibromyalgia	Level of evidence: 1a, Grade A, Weak for (100% agreement)
Tramadol (ULTRAM)	Formulary	No	Off-label for fibromyalgia	Level of evidence: 1b, Grade A, Weak for (100% agreement)
Cyclobenzaprine (FLEXERIL)	Formulary	No	Off-label for fibromyalgia	Level of evidence: 1a, Grade A, Weak for (75% agreement)

VHA POTENTIAL PLACE IN THERAPY OF FIBROMYALGIA

1. Fibromyalgia (FM) is a chronic disorder characterized by widespread muscle and joint pain, stiffness, and tenderness. It affects approximately 1% to 5% of the general population; there are approximately 60,000 veterans in the VA system with diagnosis of FM. FM is often accompanied by fatigue, sleep disturbances, mood disorders, and comorbid conditions such as irritable bowel syndrome, chronic fatigue syndrome, and headaches.
2. Clinical guidelines prioritize non-pharmacological therapies (physical activity and exercise, CBT-based approaches, patient education) for FM treatment. Pharmacologic options can be used to try and target the symptoms of FM (pain, fatigue, poor sleep and cognitive issues). Cyclobenzaprine SL tablets modestly reduced pain compared to placebo, with notable improvements in sleep and fatigue, which may be clinically relevant for those with sleep impairments.
3. Cyclobenzaprine IR (FLEXERIL) is FDA approved for acute musculoskeletal spasms. For FM patients, it improves sleep quality and slightly reduces pain. The main difference between IR and SL tablets is pharmacokinetics. Cyclobenzaprine SL is meant for bedtime use, targeting non-restorative sleep with faster absorption and higher bioavailability. It reduces systemic side effects and next-day sedation by producing less active metabolite, norcyclobenzaprine.
4. Long-term safety data for cyclobenzaprine SL in patients with FM are currently unavailable. Further research is required to assess its safety profile in individuals with hypertension, cardiovascular disease, and major psychiatric disorders. Comparative studies are also necessary to evaluate cyclobenzaprine SL against other treatments for FM to establish its therapeutic role.
5. Cyclobenzaprine SL has not shown clear efficacy advantages over other FDA-approved FM treatments (duloxetine, pregabalin, milnacipran) or select off-label agents with fair-quality evidence (amitriptyline, fluoxetine, gabapentin, and paroxetine). No head to head trials have compared cyclobenzaprine SL directly with these therapies, limiting comparative conclusions. Milnacipran remains non-formulary without CFU, though current prescription and PADR reviews indicate it is used judiciously for FM treatment. Opioids, benzodiazepines, corticosteroids and NSAIDS are NOT recommended.
6. There is insufficient evidence to broadly support any one of these therapies over another. Cyclobenzaprine SL may be considered when formulary treatments have been trialed without adequate response, with intolerable side effects or are not clinically appropriate. A trial with cyclobenzaprine IR at bedtime may be considered prior to non-formulary options. Non-formulary agents, such a milnacipran or cyclobenzaprine SL, may then be evaluated based on safety, efficacy and cost.

References

1. Tonmya (cyclobenzaprine HCl) sublingual tablets [prescribing information online]. Chatham, NJ: Tonix Medicines, Inc.; 2025.
2. Lederman S, Arnold LM, Vaughn B, et al. Pain Relief by Targeting Nonrestorative Sleep in Fibromyalgia: A Phase 3 Randomized Trial of Bedtime Sublingual Cyclobenzaprine. Pain Medicine. 2025:pnaf089. doi:10.1093/pm/pnaf089.
3. Lederman S, Arnold LM, Vaughn B, et al. Efficacy and Safety of Sublingual Cyclobenzaprine for the Treatment of Fibromyalgia: Results from a Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Care & Research. 2023;75(11):2359-2368.
4. Maggi BG, Lima NL, Correa de Lara, LH, et al. Efficacy and Safety of TNX-102 SL in Patients with Fibromyalgia: a Systematic Review and Meta-Analysis. Pain Management. 2025; 15(12): 1055-1063.
5. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR Revised Recommendations for the Management of Fibromyalgia. Ann Rheum Dis. 2017;76:318-328.

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