

Venlafaxine Shortage

Shortages of venlafaxine 37.5 mg XR capsules have been reported.

Table 1: Suppliers of venlafaxine¹

Product	Strength	DIN	MFR	Product	Strength	DIN	MFR
ACT Venlafaxine XR	37.5 mg	02304317	ACV	Ran-Venlafaxine XR	37.5mg	02380072	RAN
	75 mg	02304325			75 mg	02380080	
	150mg	02304333			150mg	02380099	
Apo-Venlafaxine XR	37.5 mg	02331683	APX	Sandoz Venlafaxine XR	37.5 mg	02310317	SDZ
	75 mg	02331691			75 mg	02310325	
	150 mg	02331705			150 mg	02310333	
Auro-Venlafaxine XR	37.5 mg	02452839	API	Teva-Venlafaxine XR	37.5 mg	02275023	TEV
	75 mg	02452847			75 mg	02275031	
	150 mg	02452855			150mg	02275058	
Effexor XR	37.5 mg	02237279	PFI	Venlafaxine XR	37.5 mg	02354713	SAN
	75 mg	02237280			75 mg	02354721	
	150 mg	02237282			150 mg	02385945	
PMS-Venlafaxine XR	37.5 mg	02278545	PMS				
	75 mg	02278553					
	150 mg	02278561					

Health Canada approved indications of venlafaxine XR²:

- symptomatic relief of major depressive disorder (MDD)
- symptomatic relief of generalized anxiety disorder (GAD)
- symptomatic relief of social anxiety disorder (SAD)
- symptomatic relief of panic disorder (PD)

Off-label uses of venlafaxine supported by guideline recommendations:

- chronic peripheral neuropathic pain³
- post-traumatic stress disorder (PTSD)⁴

Management Options

Assess Need for Continued Pharmacological Treatment for Depression

- Psychotherapies including cognitive behavioural therapy and interpersonal therapy are as effective, and in some cases may be more effective, than antidepressants for *mild to moderate* major depression.^{5,6}
- Patients with major depression who may be candidates for discontinuation of antidepressant therapy include^{5,7}:
 - those with history of an episode that has been successfully treated and in which maintenance therapy has continued for an additional 6 to 9 months.
 - those with history of two episodes that have been successfully treated and in which maintenance therapy has continued for an additional 2 to 3 years following remission of the second episode.

On account of its short half-life, venlafaxine may be associated with more severe discontinuation syndrome than other antidepressants.⁶
(See Sidebar: Tapering)

Assess Need for Continued Pharmacological Treatment for Anxiety/PTSD

- Maintaining pharmacologic therapy for at least one year reduces rate and time to relapse.⁸
- Cognitive behavioural therapy (CBT), exposure therapy and mindfulness-based therapies have been shown to be effective for managing anxiety disorders.⁹
- CBT delivered via internet is an alternative if traditional face-to-face CBT is not an option.⁹

Pharmaceutical Alternatives

- Consider increasing or decreasing the dose to the next available strength; choose based on patient history with higher/lower doses regarding effectiveness and tolerability as well as current clinical situation.
- The stability of a 15 mg/ml compounded suspension has been investigated. The suspension was compounded by using a high-speed blender to reduce the contents of extended release venlafaxine capsules (Novopharm) to a powder. The contents were incorporated into a mixture of equal parts (1:1) Ora-Plus and Ora-Sweet or incorporated into simple syrup. When packaged in amber plastic bottles, both formulations were stable for 28 days when stored at either 5°C or 23°C.¹⁰
 - Venlafaxine compounded suspension is an immediate release formulation which requires dividing the total daily dose to a q8h or q12h dosing regimen.¹⁰

Therapeutic Alternatives

- Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI).
- Other SNRIs available in Canada include desvenlafaxine, duloxetine, and levomilnacipran.
 - Desvenlafaxine is the principle active metabolite of venlafaxine¹¹ and the two are considered to have similar effects on neurotransmitters and receptors.¹² It is not approved for anxiety disorders,¹³ though some small studies in patients with MDD and comorbid anxiety disorders have suggested desvenlafaxine may be effective in anxiety.¹⁴⁻¹⁶ It is not a benefit on the Saskatchewan Drug Plan and Extended Benefits Branch (SDPEBB)¹⁷ nor Non-Insured Health Benefits (NIHB)¹⁸ formularies and a month's supply of 50 mg costs ~\$100 compared to ~\$15 for venlafaxine XR 37.5 mg.¹⁹
 - Levomilnacipran also is not a benefit of the SDPEBB¹⁷ or NIHB¹⁸ formularies and the cost of the lowest usual dose is ~\$150 per month.¹⁹ It is considered a 2nd line agent for depression⁶ and is not used for anxiety disorders.^{9,20}
 - Duloxetine is a benefit of both formularies^{17,18}; a month's supply costs ~\$30 (30 mg) or \$45 (60 mg).¹⁹
- Norepinephrine effects of venlafaxine become more prominent with daily doses above 150 mg.¹² When venlafaxine is taken at doses ≤ 150 mg, the drug may act more similarly to SSRIs in terms of neurotransmitter activity.
- Choose agents based on:
 - patient's history of previous drug trials
 - drug interactions
 - comorbid conditions
 - place in therapy (See Table 2)
 - with the exception of levomilnacipran, all SSRIs and SNRIs are considered first line for depression.⁶
 - escitalopram, paroxetine and sertraline have evidence for remission and reduction of symptoms of generalized anxiety disorder (GAD).²¹
 - all SSRIs are appropriate options for anxiety disorders.^{9,20}
 - duloxetine is the only alternative SNRI approved for use in anxiety disorders.^{9,20,21}
 - cost/patient preference

Tapering²⁶

- A general rule of thumb is to reduce the dose by 25% every 1-2 weeks.
- Some may need to extend dose reductions to every 4-6 weeks.
- Some patients may not tolerate stopping after daily doses of 37.5 mg.
 - Consider using compounded suspension to taper dose more slowly; daily doses of the suspension need to be administered as 2 or 3 equally divided doses.
 - Increase the dosing interval of XR capsules to every 2nd day then every 3rd and so on.

Switching to an Alternative Antidepressant

- Switching guidelines recommend starting the new agent once reaching venlafaxine 37.5 mg daily; with this strength unavailable, the switch may have to occur from a higher venlafaxine dose.^{22,23}
- Replacing venlafaxine with an alternative SNRI or SSRI should mitigate, but may not completely prevent, discontinuation symptoms.²⁴ Monitor the patient for discontinuation syndrome. (See [Sidebar: Monitoring](#))

Should other strengths of venlafaxine become unavailable

- When switching to another SNRI, the taper, stop, switch strategy is recommended.^{12,20,23,24} (See [Sidebar: Switching](#))
- The most commonly recommended strategies to switch from SNRIs to SSRIs are a cross-taper^{12,20} or taper, stop, switch^{12,20,23,24} See [Sidebar: Switching](#)
- Depending on the starting dose of venlafaxine, it may take 1-4 weeks to taper, which may not be possible, depending on strength availability.
- When tapering is not possible, the next best alternative will be to directly switch to a comparable dose of an alternate agent. There are no exact equivalent doses; use dosing ranges and professional judgment. If the clinical situation allows, in most cases it is preferable to start at the lower end of the dosing range of the new agent and titrate to help prevent adverse effects. (See [Table 2](#) for ranges.)
- Monitor the patient during the switch/taper for signs of discontinuation syndrome or serotonin syndrome. (See [Sidebar: Monitoring](#))

Switching ^{12,20}
See www.switchrx.ca for switching strategies.
Cross Taper
The original agent is tapered while the new agent is added simultaneously and titrated. Cross-tapers often are completed over 1-2 weeks, but may need to be longer depending on patient tolerability.
Taper, Stop, Switch
Venlafaxine is tapered to the lowest dose (37.5 mg daily). After maintaining the lowest dose for 1-2 weeks, stop the venlafaxine and start the new agent the following day at the lowest dose; titrate to effect and tolerability.

Monitoring		
Discontinuation Syndrome ^{9,26}		Serotonin Syndrome
With venlafaxine, symptoms likely will start within several days of stopping and typically will subside (without intervention) within 3 weeks. Symptoms may be alleviated by: <ul style="list-style-type: none"> • Reinstating venlafaxine and tapering more slowly (when possible). • Starting another SNRI or SSRI. 		<ul style="list-style-type: none"> - Unlikely to be a problem when switching among low doses - More of a concern when cross-tapering or directly switching at higher doses.
Typical Symptoms (FINISH ²⁶)	Others	Typical Symptoms ^{9,27,28}
<ul style="list-style-type: none"> • flu-like symptoms (chills/fever, headache, fatigue, malaise, myalgia) • insomnia • nausea/vomiting • imbalance • sensory disturbances • hyperarousal 	<ul style="list-style-type: none"> • agitation • aggression • irritability • diarrhea • dizziness/disorientation 	Neuromuscular: tremor, clonus, hyperreflexia, restlessness, rigidity Autonomic hyperactivity: ↑ bowel sounds, fever, mydriasis, diaphoresis, tachycardia, ↑ or ↓BP Mental status changes: agitation, anxiety, confusion, delirium, hallucinations, hypomania

Venlafaxine is used off-label for chronic peripheral neuropathic pain.^{3,20,30}

- The Canadian Pain Guidelines consider the SNRIs venlafaxine and duloxetine, as well as TCAs and gabapentinoids first-line therapy for chronic peripheral neuropathic pain.³
- If possible, the easiest solution would be to switch to duloxetine or a TCA. See side bar for switching strategies.
- If gabapentinoids are the only feasible option, ideally the venlafaxine would be tapered while titrating the gabapentinoid.
 - Should tapering venlafaxine not be an option, consider temporarily replacing venlafaxine with fluoxetine 10 mg x 1 week to prevent discontinuation syndrome keeping in mind potential drug interactions due to fluoxetine's strong CYP 2D6 inhibition.

Venlafaxine is used off-label for PTSD⁴

- Both venlafaxine and paroxetine are supported by evidence in meta-analyses for use in PTSD^{31,32} and, if possible, paroxetine may be the preferred agent.
- Fluoxetine and sertraline may also be effective for PTSD though their evidence is conflicting.
- Other agents than can be considered but have little data to support their use include mirtazapine and fluvoxamine.

Table 2: Dose Ranges of SSRIs and SNRIs

Agent	Usual Daily Dose Range ^{6, 9, 20}		Place in Therapy ^{6,9,21} (All 1 st line for depression, except levomilnacipran)
	Depression	Anxiety ^{¥ 9,21,25}	
Selective Serotonin Reuptake Inhibitors			
Citalopram	20-40 mg		PD, GAD, SAD
Escitalopram	10-20 mg		PD, GAD, SAD
Fluoxetine	20-40 mg	20-60 mg	PD, SAD
Fluvoxamine	100-200 mg	100-300 mg	PD, SAD
Paroxetine	20-40 mg	20-60 mg	PD, GAD, SAD
Paroxetine CR	25-50 mg (12.5-25 mg) ²⁰	12.5-75 mg	PD, GAD, SAD
Sertraline	50-200 mg		PD, GAD, SAD
Serotonin-Norepinephrine Reuptake Inhibitors			
Venlafaxine	37.5-225 mg	75-300 mg	GAD, SAD
Desvenlafaxine	50 mg	50-100 mg	GAD*
Duloxetine	30-60 mg	60-120 mg	GAD, PD [^]
Levomilnacipran	40-120 mg	-	Depression: 2 nd line
CR= controlled release; GAD = generalized anxiety disorder; PD=panic disorder; SAD=social anxiety disorder			
¥ Doses differ depending on anxiety type.			
*Based on limited and mostly retrospective evidence. ^{15,16}			
[^] Based on limited, open-label evidence. ²⁹			

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