

Tamoxifen Shortage

Table 1: Suppliers of tamoxifen citrate¹

Product	Strength	DIN	MFR
Nolvadex-D	20 mg	02048485	AST
Apo-Tamox	10 mg	00812404	APX
	20 mg	00812390	
Teva-Tamoxifen	10 mg	00851965	TEV
	20 mg	00851973	

Background

The current supply of tamoxifen 10 mg and 20 mg tablets is insufficient to meet Canadian demand largely because of manufacturing issues with Apotex and Teva.² All manufacturers are working to resume regular production and efforts are being made to increase supply through alternate means (e.g. importation).³ In the meantime, shortages may be experienced. **This document has been written for Saskatchewan users and may not be applicable in other jurisdictions.**

Currently, McKesson Regina has no tamoxifen inventory.⁴ The Saskatchewan Cancer Agency (SCA) is implementing conservation strategies but should have sufficient supply to meet demand of its patients for several months,⁵ which may be adequate until market supply is corrected. The current shortage is expected to be resolved by the end of January 2020.

Health Canada approved indications of tamoxifen⁶:

- adjuvant treatment of early breast cancer in women with estrogen-receptor positive tumours
- treatment of women with hormone responsive locally advanced/ metastatic breast cancer

Indications of tamoxifen funded by SCA for Saskatchewan patients⁷:

- *Breast Cancer – Adjuvant*
 - endocrine therapy in pre or post-menopausal women or men with hormone-receptor positive invasive disease either initially for 5 to 10 years (upfront strategy), or for 2 to 3 years prior to 2 to 3 years of treatment with an aromatase inhibitor for a total of 5 years (switch strategy) of hormonal therapy
 - endocrine therapy in pre or post-menopausal women with hormone-receptor positive ductal carcinoma in-situ (DCIS) for up to 5 years
- *Breast Cancer – Metastatic*
 - endocrine therapy in pre or post-menopausal women with hormone-receptor positive breast cancer
- *Gynecology*
 - treatment of recurrent or progressive endometrial, epithelial ovarian, fallopian tube or primary peritoneal cancer as a single agent after failure or contraindication to standard therapy
- *Sarcoma*
 - treatment of recurrent desmoid tumor or aggressive fibromatosis patients for whom other treatment modalities are not available

Off-label uses of tamoxifen⁸:

- prevention of breast cancer in women with no previous diagnosis of breast cancer⁷ (FDA-approved⁸, not Health Canada-approved⁶ and not an indication covered by SCA⁷)

Management Options

Refer to SCA if Applicable

- See indications funded by SCA above.
- Some patients may be filling tamoxifen in community even though they are eligible to receive it through SCA.
 - confirm indication and duration (if being used as adjuvant endocrine therapy for breast cancer) of treatment
 - prescriptions must be written by an SCA oncologist or primary care provider to whom care has been transferred

Therapeutic Alternatives

Primary prevention of breast cancer

- Reducing obesity,⁹ increasing physical activity,¹⁰ and reducing alcohol intake¹¹ are measures individuals can take to reduce breast cancer risk.
- Consider that in **high risk** women, use of selective estrogen reuptake modulators (SERMs) or aromatase inhibitors (AIs) have been shown to reduce the incidence of new primary breast cancers, **but there is no evidence that this reduces breast cancer-related or overall mortality.**^{12,13}
 - The definition of high risk varies; the following may be considered high risk women¹²:
 - age > 60
 - history of lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), or atypical proliferative lesion of the breast (atypical ductal or lobular hyperplasia)
 - women between 35 and 59 years with estimated risk of breast cancer of 1.66 percent or higher over five years from the Gail model (www.cancer.gov/bcrisktool/)
 - individuals with BRCA 1 and 2 mutations
- Off-label chemoprophylaxis may be considered in these high-risk women based on benefits and risks of SERMs/AIs as well as the patient's values.
 - this is a good opportunity to reassess benefits and risks as well as to reconfirm patient's desire for chemoprophylaxis
- Duration of prophylaxis in studies has been 3 to 5 years and benefits of tamoxifen have been shown to persist up to 8 years after discontinuation.¹⁴
 - assess if patient is candidate for discontinuation
 - **patients who are taking tamoxifen for breast cancer prevention can be reassured short-term interruption is unlikely to be clinically significant**

Postmenopausal women

- Available prophylactic agents:
 - Selective Estrogen Reuptake Modulators (SERMs)
 - tamoxifen, raloxifene
 - Aromatase Inhibitors (AIs)
 - anastrozole, exemestane
 - letrozole is not considered for this indication¹⁴

Note that none of these agents is indicated for prophylaxis by Health Canada^{6,15-17}; tamoxifen and raloxifene have FDA indications for breast cancer risk reduction.⁸

- Benefits¹⁴:
 - Number of cases per 1000 women of estrogen-receptor positive (ER+) breast cancer reduced by endocrine therapy over 5 years (95% confidence interval)¹⁸:
 - tamoxifen: 16 (8-24)
 - raloxifene: 8 (4-13)
 - aromatase inhibitors: 15 (8-20)
 - Fracture:
 - tamoxifen is associated with fewer nonvertebral fractures compared to placebo
 - raloxifene is associated with fewer vertebral fractures compared to placebo
- Harms:
 - Tamoxifen
 - ↑ risk of venous thromboembolic events (VTE), endometrial cancer and cataracts¹⁴

- other adverse effects: vasomotor symptoms, vaginal bleeding, dyslipidemia, depression, arthralgia/myalgia¹⁹
- Raloxifene
 - ↑risk of VTE, though less than tamoxifen¹⁴
 - other adverse effects: vasomotor symptoms, edema, arthralgia/myalgia⁸
- Aromatase inhibitors:
 - loss of bone density and osteoporosis
 - studies in breast cancer treatment vs. tamoxifen indicate ↑fracture rate; may not be generalizable to this population¹⁴
 - other adverse effects: arthralgia/myalgia, vasomotor symptoms, vaginal dryness, hypercholesterolemia, edema, nausea^{20,21}
- Doses for prevention of breast cancer⁸:
 - tamoxifen 20 mg orally once daily; raloxifene 60 mg orally once daily; anastrozole 1 mg orally once daily; exemestane 25 mg orally once daily

Premenopausal women

- Tamoxifen is the only endocrine agent considered in this population:
 - No data are available regarding effectiveness of raloxifene for prevention of breast cancer in premenopausal women¹³ and it is contraindicated in women of childbearing potential.¹⁶
 - AIs are not recommended in premenopausal women.^{20,21}

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