Drug Monograph

A - Drug Name

tamoxifen

SYNONYM(S): ICI-46474; TAM

COMMON TRADE NAME(S): Nolvadex®-D

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B - Mechanism of Action and Pharmacokinetics

Tamoxifen is a synthetic non-steroidal anti-estrogenic analog. It is thought to competitively block estrogen receptors and suppress the genome of the breast cancer cell. It also has low affinity to the androgen receptor. Tamoxifen displays estrogenic-like effects on several body systems including the endometrium, bone and blood lipids, and may have growth inhibitory effects that are not anti-estrogenic. Tamoxifen increases the risk of endometrial cancer, uterine sarcoma, arterial and venous thromboembolism and is not approved for use in Canada to prevent breast cancer. Requires activation to endoxifen; patients taking concomitant medications that inhibit CYP2D6 or with certain polymorphisms of CYP2D6 may have subtherapeutic levels.

Absorption	Oral absorption: Well absorbed orally Steady state of tamoxifen is generally reached after 3-4 weeks.	
Distribution	High concentrations in uterus, endometrium, breast tissues, distribution also observed in lung, liver, kidneys, and pancreas.	
	Cross blood brain barrier?	Higher levels of tamoxifen and metabolites observed in brain metastases than normal brain tissue
	PPB	>98%
Metabolism	Prodrug, requires activation to endoxifen. Metabolized by CYP2D6 or 3A4	

	pathways to 4-hydroxytamoxifen or N-desmethyltamoxifen, then to endoxifen. CYP2B6, 2C8, 2C9, and 2C19 play a minor role. Tamoxifen is an inhibitor of p-glycoprotein. Autoinduction has been described.	
	Active metabolites	N-desmethyltamoxifen, 4-hydroxytamoxifen, endoxifen
	Inactive metabolites	Yes
Elimination	Secreted in bile, undergoes enterohepatic circulation, 65% of the dose slowly excreted in feces over 2 weeks, mainly as polar conjugates.	
	Urine	9 to 13%
	Half-life	Parent drug: 5-7 days N-desmethyltamoxifen: 9-14 days

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C - Indications and Status

Health Canada Approvals:

- Adjuvant treatment of breast cancer (estrogen receptor positive tumours) in women
- Treatment of hormone responsive locally advanced or metastatic breast cancer in women

Other Uses:

- Gynecological cancers (endometrial, ovarian)
- Desmoid tumours

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: Not applicable

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (<10%)	D
	Venous thromboembolism (<10%)	D
Dermatological	Alopecia (<10%)	E
	Other (porphyria cutanea tarda, cutaneous lupus erythematosus - rare)	E
	Radiation recall reaction (rare)	I
	Rash (>10%; in rare cases may be severe)	E
Gastrointestinal	Constipation (<10%)	E
	Diarrhea (<10%)	E
	Nausea, vomiting (>10%)	I
General	Edema , fluid retention (>10%)	E
	Fatigue (>10%)	I E D
	Tumour flare (<10%) (rare ↑ calcium early in therapy)	E
Hematological	Myelosuppression (<1%, usually mild, including platelets)	E
Hepatobiliary	↑ LFTs (<10%, rarely severe)	D
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (<10%)	I
Metabolic / Endocrine	↑ Ca	I E
	↑ Triglycerides (<10%)	D
Musculoskeletal	Musculoskeletal pain (<10%)	E
Neoplastic	Secondary malignancy (including endometrial cancer, uterine sarcoma - rare)	D
Nervous System	Depression (<1%)	D
	Dizziness (<10%)	E
	Dysgeusia (<1%)	I
	Headache (<10%)	E
	Optic neuritis (<1%)	D
	Paresthesia (<10%)	E
Ophthalmic	Cataract (<10%)	D
	Eye disorders (corneal changes - rare)	D
	Retinopathy (<10%)	D

Reproductive and breast disorders	Endometrial hyperplasia , polyps (<10%)	D L
	Estrogen deprivation symptoms (>10%)	E
	Irregular menstruation	D
	Other (ovarian cysts, uterine fibroids, vaginal polyps: <10%)	D L
	Vaginal bleeding or discharge (>10%)	E
Respiratory	Pneumonitis (rare)	D
Vascular	Vasculitis (cutaneous; rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Tamoxifen is usually **well-tolerated** and serious side effects are rare. The most frequent side effects are **hot flashes, nausea and vomiting**. These may occur in up to 25% of patients and are rarely severe enough to discontinue treatment. Patients who have their sleep interrupted by drenching night sweats may benefit by taking tamoxifen in the morning. Clonidine (0.1mg daily), venlafaxine (75 mg daily) and gabapentin (titrated to 300 mg TID) have been shown to help reduce the number of hot flashes in some studies.

In some patients, a transient increase in bone pain, local disease flare (swelling and redness) and/or hypercalcemia may occur at the initiation of therapy in patients with metastatic disease (**tamoxifen flare response**). Treatment should continue for a minimum of 3 to 4 weeks to rule out tumour flare response. Serum calcium should be monitored for a few weeks, starting 3-7 days after starting treatment in patients with extensive bony metastatic disease.

The risk of **endometrial cancer** increases following tamoxifen therapy and may be related to the estrogen-like effect of tamoxifen. An increase in uterine sarcomas was also reported in prevention trials. Pelvic complaints, such as unusual vaginal bleeding, unusual pelvis pain/pressure should be promptly evaluated in patients taking tamoxifen.

Decreases in **platelets** (usually to 80-90 x 10^9/L) or leukocytes have been observed, but no bleeding has been reported. In clinical trials, the incidence of **myalgia** was similar between patients treated with tamoxifen or an aromatase inhibitor.

Tamoxifen is associated with increased rates of **thromboembolic events**, including stroke, deep vein thrombosis, pulmonary embolism, and microvascular thrombosis after breast reconstruction surgery. Higher rates of complications were observed in a retrospective study with patients who were taking tamoxifen within 28 days of delayed breast reconstruction, which included total flap loss due to either venous or arterial thrombosis.

Ocular problems (retinopathy, cataracts, corneal opacities, optic neuritis) have been reported in

patients.

Radiation recall reaction was usually reversible when tamoxifen was held, and milder upon re-challenge. Treatment with tamoxifen was continued in most cases.

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E - Dosing

Refer to protocol by which patient is being treated. Patients with advanced disease are usually treated until progression, and patients being treated with adjuvant intent for 5 years.

Adults:

Oral: 20 - 40 mg daily in single or divided doses

Dosage with Toxicity:

Toxicity	Action
Severe estrogen depletion symptoms	Consider short drug holiday and rechallenge
Arterial/Venous thromboembolism	Discontinue
Severe depression	Discontinue
Pancreatitis, pneumonitis, hepatotoxicity, severe hypercalcemia	Discontinue
Cataracts, retinopathy, corneal changes, severe myalgia	Consider discontinuing
Severe skin symptoms, porphyria cutanea tarda, cutaneous lupus erythematosus	Discontinue
Microvascular breast reconstruction	Consider temporary hold

Dosage with Hepatic Impairment:

Adjustment required, no details found

Dosage with Renal Impairment:

No adjustment required

Dosage in the elderly:

No adjustment required.

Children:

Not recommended as safety and efficacy have not been established.

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F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- Swallow whole with a glass of water, with or without food.
- Do not crush or chew the tablets.
- Take the dose at about the same time each day.

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G - Special Precautions

Contraindications:

- Patients with hypersensitivity to tamoxifen or any of its components.

Other Warnings/Precautions:

- Use with extreme caution in patients with a history of significant thromboembolic disease.
- Some brands of tamoxifen contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Use with caution in patients with pre-existing myelosuppression or depression.
- Consider temporary hold in patients undergoing delayed microvascular breast reconstruction.
- Tiredness and weakness have been reported. Caution when driving and operating machinery while such symptoms persist.

Other Drug Properties:

- Carcinogenicity: Documented in animals

Pregnancy and Lactation:

- Genotoxicity: Documented in animals
- Embryotoxicity: Likely
  Changes similar to those seen with DES have been reported in models of fetal development
- Fetotoxicity: Likely
  Tamoxifen is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for **9 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Unknown

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H - Interactions

Tamoxifen is a substrate of CYP 3A (major), 2D6 (major), 2C8/9, 2C19, 2B6. Inducers (and inhibitors) of these enzymes can theoretically increase (and decrease) the metabolism of tamoxifen and the formation of its metabolites.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Oral anticoagulants (e.g : warfarin)	↑ Significant increase in anticoagulant effect	Unknown	Monitor prothrombin time; adjust anticoagulant dose as required

Thyroid function test	↑ T4 (thyroxine)	↑ thyroxine-binding globulin	None, thyroid function does not appear to be affected
Drugs metabolized by P450 oxidases or p-glycoprotein	Altered effects; ↓ metabolism of enzyme substrates	Tamoxifen inhibits P450 oxidases or p-glycoprotein	Caution
Mitomycin	↑ risk of hemolytic uremic syndrome	Unknown	Avoid concomitant use
Bromocriptine	Potentially ↑ side effects of tamoxifen	↑ serum levels of tamoxifen and metabolites	Caution
Drugs prolonging QT	Prolongation of QT	Possible additive effects with tamoxifen	Avoid concomitant use
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ effects of tamoxifen	↑ metabolism	Caution
Other drugs metabolised by CYP 3A4	↓ effect of CYP3A4 substrates	Tamoxifen may induce CYP 3A4	Avoid concomitant use
Anastrozole	↓ concentrations of anastrozole (27%)	Unknown	Do not co-administer since no efficacy or safety benefit
Letrozole	↓ plasma concentrations of letrozole (38%)	Unknown	Avoid concomitant usage as no efficacy or data available
Potent CYP2D6 inhibitors (i.e. fluoxetine, paroxetine, quinidine, pimozide, perphenazine, terbinafine, etc)	↓ plasma concentration of tamoxifen active metabolite	Inhibits CYP2D6 metabolism of tamoxifen	Avoid concomitant use
Moderate CYP 2 D6 inhibitors (i.e. desipramine, haloperidol, citalopram,	↓ plasma concentration of tamoxifen active metabolite	Inhibits CYP2D6 metabolism of tamoxifen	Caution, consider alternative drug options

sertraline, hydroxyzine, amlodipine, ritonavir)			
Low CYP 2D6 activity (in patients with certain CYP2D6 alleles)	↓ plasma concentration of tamoxifen active metabolite	Inhibits CYP2D6 metabolism of tamoxifen	Monitor treatment response; routine pharmacogenomics screening is currently not recommended

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Calcium, in patients with extensive bone metastases; for first few weeks then periodic	
Clinical assessment of toxicity - vaginal bleeding, ocular, thromboembolism, myalgia, tumour flare, GI and pulmonary effects, rash, etc.	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and periodic
Triglycerides and cholesterol in patients with pre-existing hyperlipidemia	Baseline and periodic

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- tamoxifen ()

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K - References

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May 2022 Updated Pregnancy/lactation section

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L - Disclaimer

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