

TAMOXIFEN



*“Mater Dolorosa” (Lady of Sorrows), painted wood sculpture, 16th century  
Pedro de Mena.*

*Let me inside you  
Into your room  
I've heard it's lined  
With the things you don't show  
Lay me beside you  
Down on the floor  
I've been your lover  
From the womb to the tomb  
I dress as your daughter  
When the moon becomes round  
You be my mother  
When everything's gone*

*And she will always carry on  
Something is lost  
But something is found  
They will keep on speaking her name  
Somethings change  
Some stay the same*

*Keep beckoning to me  
From behind that closed door  
The maid and the mother  
And the crone that's grown old*

*I hear your voice  
Coming out of that hole  
I listen to you  
And I want some more  
I listen to you  
And I want some more*

*She will always carry on  
Something is lost  
But something is found  
They will keep on speaking her name  
Some things change  
Some stay the same*

*She will always carry on  
Something is lost  
But something is found  
They will keep on speaking her name  
Some things change  
Some stay the same*

*Let me inside you  
Into your room*

*I've heard it's lined  
With the things you don't show  
Lay me beside you  
Down on the floor  
I've been your lover  
From the womb to the tomb  
I dress as your daughter  
When the moon becomes round  
You be my mother  
When everything's gone*

*And she will always carry on  
Something is lost  
But something is found  
They will keep on speaking her name  
Some things change  
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*She will always carry on  
Something is lost  
But something is found  
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*And she will always carry on  
Something is lost  
But something is found  
They will keep on speaking her name  
Some things change  
Some stay the same*

*Hymn to Her, Chrissie Hynde, The Pretenders, 1986*

*Whether Christian, Jew, Muslim, Hindu, Taoist, or Buddhist could there be any more universal symbol of sadness, the eternal struggle that is the human condition, than Pedro de Mena's Mater Dolorosa? But somehow it is also a positive and comforting symbol, the eternal feminine, motherhood - though something is lost, there is yet always hope for something found, and despite the darkest of nights, she will always carry on, we keep on speaking her name, she will still be our mother, when everything's gone.... some things change, some stay the same....*

# TAMOXIFEN

## Introduction

**Tamoxifen** is a *selective* estrogen receptor modulator (**SERM**).

It is an antagonist of the estrogen receptor in breast tissue via its active metabolite, 4-hydroxytamoxifen.

In *other* tissues however such as the endometrium, it behaves as an **agonist**, and thus may also be characterized as a mixed agonist/antagonist of estrogen.

Tamoxifen is used as:

- Adjuvant anti-estrogen therapy in breast cancers that are hormone receptor-positive.
- In selected cases as primary prevention of breast cancer in high-risk women

**Of particular relevance to Emergency Department presentations, tamoxifen carries a risk for:**

- **VTE disease**
- **Uterine cancer**
- **Gall stone development.**

## History

The compound ICI 46,474 was developed by **Dr. Dora Richardson**, an organic chemist at ICI, (Imperial Chemical Industries) in 1967.

It was originally intended to be a contraceptive agent, though successful in this regard in animal studies, it was not successful in human studies.

The failed contraceptive, however reinvented itself when it was found to be an effective agent for the prevention of breast cancer, in the early 1970s.

In 1973 compound ICI 46,474, was introduced into clinical practice as tamoxifen.

## Chemistry

Tamoxifen, a synthetic, non-steroidal, trans-isomeric derivative of triphenylethylene.

## Classification

There are 3 currently available SERMs:

1. **Tamoxifen**
2. Raloxifene
3. Toremifene

### Preparation

Tamoxifen as:

#### Tablets:

- 10 mg
- 20 mg.

### Mechanism of Action

Tamoxifen displays a complex spectrum of estrogen antagonist and estrogen agonist-like pharmacological effects in different tissues.

It competes with estrogen for receptor sites in **breast tissue** (i.e an **anti-estrogenic** effect)

In **receptor positive breast cancer patients**, at the tumour level, tamoxifen acts primarily as an anti-estrogen, preventing estrogen binding to the estrogen receptor and inhibiting tumour growth.

However is there is estrogen *agonist* activity on:

- Endometrium
- Bone
- Lipids.

### Pharmacokinetics

#### Absorption:

- Tamoxifen is given orally.

#### Distribution:

- Tamoxifen is very highly protein bound to serum albumin (> 99%)
- Tamoxifen can cross the human placenta.

- It is unknown if tamoxifen is excreted into breast milk.

### Metabolism and excretion:

- Tamoxifen undergoes extensive metabolism in the liver by CYP3A4 and CYP2D6.

The major circulating metabolite of tamoxifen in humans is desmethyl-tamoxifen which has a pharmacological profile very similar to that of tamoxifen and thus contributes to the therapeutic effect.

Other minor metabolites are formed, some of which also have anti-oestrogenic activity.

- The elimination of tamoxifen and its major metabolite N-desmethyl-tamoxifen is slow.

The elimination half-life of tamoxifen is prolonged at 5 -7 days, and 10 - 14 days for N-desmethyltamoxifen.

This leads to extensive accumulation of both compounds in serum during chronic administration.

### Indications

Tamoxifen is used as:

1. Adjuvant anti-estrogen therapy in breast cancers that are hormone receptor-positive.
  - It is ineffective as adjuvant therapy in hormone receptor-*negative* tumours
2. In selected cases as primary prevention of breast cancer in high-risk women:
  - Tamoxifen taken for **5 years** reduces the risk of oestrogen receptor-positive breast cancer (but not oestrogen receptor-negative tumours) in women at high risk, e.g. a family history of breast cancer.

The reduced risk also persists for at least 5 years *after* stopping tamoxifen.

### Contra-indications / Precautions

These include:

1. Tamoxifen must not be given during pregnancy:

- Women should ensure effective contraception during treatment and for 2 months after stopping.
2. Patients with pre-existing endometrial hyperplasia:
    - Tamoxifen (and SERMs in general) increase risk of endometrial cancer.
  3. Previous thromboembolic disease:
    - There is an increased risk of thromboembolic disease (and with SERMs in general)
  4. Hormone receptor negative tumours:
    - Not indicated - with risk of adverse reactions
  5. Chemotherapy combined with tamoxifen (or a SERM in general):
    - This may further increase the risk of thrombosis (consider prophylactic anticoagulants).
  6. Hypersensitivity to tamoxifen
  7. Liver disease:
    - As the main site of metabolism is the liver, and accumulation of the drug and its active metabolites is possible with prolonged treatment, dose and dosing interval may need adjustment in patients with hepatic disease.
  8. Pregnancy / breast feeding (contraindicated, see below)

### Pregnancy

Tamoxifen may increase the risk of congenital abnormalities and so is **contraindicated** in pregnancy.

Animal studies have demonstrated adverse effects to the fetus, as well as fetal loss following tamoxifen exposure during pregnancy.

Human experience with fetal exposure to tamoxifen is very limited. Both normal and malformed infants have been reported following the use of tamoxifen during pregnancy. Case reports of craniofacial malformations including Goldenhar syndrome and Pierre Robin sequence have been associated with the use of tamoxifen during pregnancy. Ambiguous genitalia in a female infant exposed to tamoxifen in utero has also been reported.

Pregnancy complications following gestational exposure to tamoxifen include oligohydramnios, spontaneous preterm birth and respiratory distress have been described.

Therefore, consider an alternative medicine during pregnancy. If tamoxifen has been used during pregnancy, monitoring of both maternal and fetal wellbeing by a multidisciplinary team is recommended.

Unfortunately, there is a lack of long-term information about children who were exposed to tamoxifen in utero.

### Breast feeding

Tamoxifen is **contraindicated** in breastfeeding, due to the potential risk of severe adverse reactions in the infant.

### Adverse Reactions

These include:

1. Hot flushes
  - Common and can be very significant.
2. Nausea
  - Common and can be very significant.
3. Night sweats
  - Can be very significant.
4. Myalgias:
  - Including leg cramps
5. Peripheral edema
6. Uterine complications:
  - Menstrual irregularities
  - Endometrial hyperplasia
  - **Endometrial cancer** (particularly in postmenopausal women)
7. Thromboembolic disease.
8. Flare reactions:



- In patients with metastatic disease, there may be a transient increase in bone and tumour pain when starting treatment. Hypercalcaemia may also occur if there are bone metastases.

9. Dermatological:

- Mild reactions:
  - ♥ Angioedema / erythema multiforme
- Occasional more serious reactions:
  - ♥ Stevens-Johnson syndrome, cutaneous vasculitis and bullous pemphigoid.

10. Hepatic:

- Raised liver enzymes - rarely more serious liver impairment.
- Gallstones:

Tamoxifen therapy can lead to gallstone formation in postmenopausal breast cancer patients and is most apparent after 3 years of treatment.<sup>5</sup>

11. Elevated serum triglyceride levels:

- Elevation of serum triglyceride levels is relatively common, occasionally associated with pancreatitis.

**Dosing**

Usual dosage is **20 mg once daily**.

References:

1. eTG - March 207
2. Tamoxifen in Australian Medicines Handbook, October 2013
3. Tamoxifen in MIMs October 2013.
4. Tamoxifen in RWH Pregnancy & Breast feeding Guidelines, 17 November 2016.
5. Mehmet L. Akin et al. Tamoxifen and Gallstone Formation in Postmenopausal Breast Cancer Patients: Retrospective Cohort Study. World J. Surg. Vol. 27, No. 4, April 2003.

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