

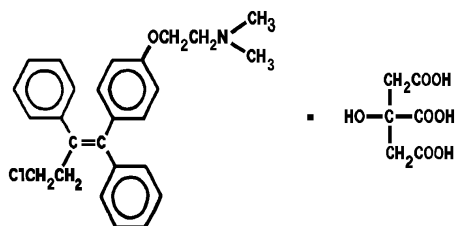
NEW ZEALAND DATA SHEET

FARESTON TABLETS

NAME OF THE DRUG

Toremifene 60 mg (present as toremifene citrate 88.5 mg)

Chemical structure



DESCRIPTION

Toremifene Citrate is a white or almost white crystalline powder. It is (Z)-4-Chloro-1,2-diphenyl-1-{4-[2-(N,N-dimethylamino)ethoxy]phenyl}-1-butene citrate. The molecular formula is C₃₂H₃₆ClNO₈. MW: 598.1 CAS registry no: toremifene citrate [89778-27-8].

FARESTON Tablets are white or almost white, round, flat, uncoated tablets with bevelled edges, embossed with TO60 on one side of the tablet.

Each FARESTON Tablet contains toremifene citrate equivalent to toremifene 60 mg, microcrystalline cellulose, lactose, maize starch, sodium starch glycollate, povidone, magnesium stearate and colloidal anhydrous silica.

PHARMACOLOGY

Toremifene is a non-steroidal triphenylethylene derivative. Like other members of this class, eg. tamoxifen and clomifene, toremifene binds to oestrogen receptors and may exert oestrogenic, anti-oestrogenic or both activities, depending upon the duration of treatment, animal species, gender, target organ and variable selected. In general, however, non-steroidal triphenylethylene derivatives are predominantly anti-oestrogenic in rats and man and oestrogenic in mice.

In female rats the lowest dose of toremifene that exerts an intrinsic oestrogenic effect on the uterus is about 40 times higher than that of tamoxifen. In the same model the lowest anti-oestrogenically effective dose is 10 times higher than that of tamoxifen suggesting a lower oestrogenic to anti-oestrogenic ratio for toremifene than for tamoxifen. No data are available on this ratio in humans. In post-menopausal volunteers receiving oestrogen by oral or transdermal routes, toremifene was shown to exert an anti-oestrogenic effect on vaginal mucosa by reducing the cornification index. The latter effect was reproducibly found for toremifene doses ranging from 20 to 200 mg daily and could not be distinguished from that of 20 mg tamoxifen. Lower doses of toremifene did not oppose the oestrogenic stimulation of vaginal epithelium.

Toremifene binds specifically to oestrogen receptors, competitively with oestradiol, and inhibits oestrogen-induced stimulation of DNA synthesis and cell replication. In some experimental cancers and/or using high-dose, toremifene displays anti-tumour effects which are not oestrogen-dependent.

The anti-tumour effect of toremifene in breast cancer is mainly due to the anti-oestrogenic effect, although other mechanisms (changes in oncogene expression, growth factor secretion, induction of apoptosis and influence on cell cycle kinetics) may also be involved in the anti-tumour effect.

CLINICAL TRIALS

Three prospective, randomised, controlled clinical studies (North American 5/044, Eastern European 5/050 and Nordic 5/049) were conducted to evaluate the efficacy of FARESTON for the treatment of breast cancer in postmenopausal women. The patients were randomised to parallel groups receiving FARESTON 60 mg (FAR60) or tamoxifen 20 mg (TAM20) in the North American study or tamoxifen 40 mg (TAM40) in the Eastern European and Nordic studies. The North American and Eastern European studies also included high dose toremifene arms of 200 and 240 mg daily, respectively. The studies included postmenopausal patients with tumour oestrogen receptor (ER) positive or ER unknown metastatic or locally advanced breast cancer. The patients had at least one measurable or evaluable lesion. The primary efficacy variables were response rate (RR), and time to progression (TTP). Survival (S) was also determined.

The studies showed similar response rates and two of the studies showed similar times to progression. The Nordic study showed a longer time to progression with tamoxifen in the tumour ER unknown group of patients. Survival in the three studies was similar between FARESTON and tamoxifen.

CLINICAL STUDIES TABLE

Study	North American		Eastern European		Nordic	
	FAR60	TAM20	FAR60	TAM40	FAR60	TAM40
Treatment Group	FAR60	TAM20	FAR60	TAM40	FAR60	TAM40
No. Patients (No. evaluable)	221 (221)	215 (215)	157 (154)	149 (145)	214 (212)	201 (193)
Responses						
CR ¹ + PR ²	14+33	11+30	4+24	2+26	19+47	16+56
RR ³ (CR + PR)%	21.3	19.1	18.2	19.3	31.1	37.3
Time to Progression (TTP)						
Median TTP (months)	5.6	5.8	4.9	5.0	7.3	10.2
Survival (S)						
Median S (months)	38.2	31.7	28.4	26.7	31.6	39.0

¹CR = Complete Response

²PR = Partial Response

³RR = Response Rate

Toremifene 200 mg daily in the North American study and 240 mg daily in the Eastern European study produced, respectively, 22.6% and 28.3% response rates, 5.7 and 6.1 month median times to progression, and 30.1 and 26.0 month median survival times.

PHARMACOKINETICS

General characteristics

Toremifene is readily absorbed after oral administration. Peak concentrations in serum are obtained within 3 (range 2-5) hours. Food intake has no effect on the extent of absorption but may delay the peak concentrations by 1.5-2 hours. The changes due to food intake are not clinically significant.

The serum concentration curve can be described by a biexponential equation. The half-life of the first (distribution) phase is 4 (range 2-12) hours, and of the second (elimination) phase 5 (range 2-10) days.

The basal disposition parameters (CL and V) could not be estimated due to the lack of an intravenous formulation. Toremifene binds extensively (>99.5%) to serum proteins, mainly to albumin. Toremifene obeys linear serum kinetics at oral daily doses between 10 and 680 mg. The mean concentration of toremifene at steady-state is 0.9 (range 0.6-1.3) µg/mL at the recommended dose of 60 mg daily.

Toremifene is extensively metabolised. In human serum the main metabolite is N-demethyltoremifene with mean half-life of 11 (range 4-20) days. Its steady-state concentrations are about double those of the parent compound. It has similar anti-oestrogenic, albeit weaker antitumour activity than the parent compound. It is bound to plasma proteins even more extensively than toremifene, the protein bound fraction being >99.9%. There is no significant potential for competition between toremifene and N-demethyltoremifene in protein binding. Three minor metabolites have been detected in human serum: (deaminohydroxy)toremifene, 4-hydroxytoremifene, and N,N-didemethyltoremifene. Although they have theoretically interesting hormonal effects, their concentration during toremifene treatment are too low to have any major biological importance.

Toremifene is eliminated mainly as metabolites in the faeces. Enterohepatic circulation of toremifene, but not its biologically active metabolites, can be expected. About 10% of the administered dose is eliminated via urine as metabolites. Owing to the slow elimination, steady-state concentrations in serum are reached in 4 to 6 weeks.

Characteristics in patients

Clinical anti-tumour efficacy and serum concentration have no positive correlation at the standard recommended daily dose of 60 mg.

No information is available concerning polymorphic metabolism. The enzyme complex known to be responsible for the metabolism of toremifene in humans is cytochrome P450-dependent hepatic mixed function oxidase. The main metabolic pathway, N-demethylation, is mediated mainly by CYP 3A4-6.

Renal insufficiency has no influence on toremifene kinetics.

Severe hepatic failure decreases the elimination rate of toremifene. The severity of hepatic failure when measured by liver enzymes does not, however, correlate with the elimination kinetics of toremifene.

INDICATIONS

FARESTON is indicated for first line treatment of hormone-dependent metastatic breast cancer in postmenopausal patients.

CONTRAINDICATIONS

Pregnancy (see "Use in Pregnancy").

Pre-existing endometrial hyperplasia and severe hepatic failure are contraindications for long-term use of toremifene.

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to toremifene, in the form of QT prolongation. For reasons of drug safety, toremifene is therefore contraindicated in patients with:

- Congenital or documented acquired QT prolongation
- Electrolyte disturbances, particularly in uncorrected hypokalaemia
- Clinically relevant bradycardia
- Clinically relevant heart failure with reduced left-ventricular ejection fraction
- Previous history of symptomatic arrhythmias.

Toremifene should not be used concurrently with other drugs that prolong the QT interval.

PRECAUTIONS

In clinical trials, FARESTON has been shown to prolong the QT/QTc interval on the electrocardiogram in a dose-related manner. The following information regarding the effects of toremifene on QT/QTc-prolongation is of special importance (also see Contraindications).

A thorough QT/QTc study was conducted in 250 healthy men to characterize the effects of toremifene on the QT/QTc interval duration. In a randomized, multiple-dose 5-arm parallel group study subjects (n=50 per treatment group) received either placebo, moxifloxacin 400 mg or toremifene 20 mg, 80 mg, or 300 mg per day. The results of this study show that toremifene causes dose related increases in QT/QTc with a mean change from baseline in QTc of 6, 24 and 57 msec in the 20 mg, 80 mg and 300 mg groups, respectively. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QT-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

FARESTON should be used with caution in patients with ongoing proarrhythmic conditions (especially elderly patients) such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (including Torsade de pointes) and cardiac arrest. If signs or symptoms that may be associated with cardiac arrhythmia occur during treatment with FARESTON, treatment should be stopped and an ECG should be performed.

If the QTc interval is > 500 msec, FARESTON should not be used.

Patients with non-compensated cardiac insufficiency or severe angina pectoris should be monitored closely.

Hypercalcaemia may rarely occur during the first week of treatment, especially in patients with bone metastases. They should be informed about the clinical symptoms of hypercalcaemia.

Patients with a history of severe thromboembolic disease should generally not be treated.

There are no clinical data available in patients with labile or poorly controlled diabetes, in patients with severely altered performance status or in patients with non-compensated cardiac insufficiency or serious angina pectoris.

Experience of the long-term use of toremifene is limited.

Patients who have known hypersensitivity to anti-oestrogens or ingredients in FARESTON tablets should not take FARESTON.

Carcinogenicity/mutagenicity

Toremifene was not genotoxic in a range of in vitro and in vivo mutagenicity, clastogenicity and DNA effect studies. Toremifene has not been found to be carcinogenic in rats. In mice, oestrogens induce ovarian and testicular tumours as well as hyperostosis and osteosarcomas. Toremifene has a species-specific oestrogen-like effect in mice and causes similar tumours. These findings are postulated to be of little relevance for the safety in humans, where toremifene acts mainly as an anti-oestrogen.

Use in Pregnancy (Category B3)

FARESTON must not be administered during pregnancy (see "Contraindications"). Toremifene is recommended for postmenopausal patients. Owing to the lack of specific data in humans, toremifene should not be used during pregnancy. In animal reproduction studies toremifene has been shown to prevent implantation, to induce parturition failures and to reduce perinatal survival. In addition, treatment during organogenesis induced changes in ossification, rib abnormalities and oedematous fetuses.

Use in Lactation

Toremifene is recommended for postmenopausal patients. Owing to the lack of specific data in humans, toremifene should not be used during lactation. In preclinical studies in rats, decreased body weight gain of the offspring during lactation was observed.

Interactions with Other Drugs

No specific interaction studies have been performed.

An additive effect on QT interval prolongation between FARESTON and the following drugs and other medicinal products that may prolong the QT interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including Torsade de pointes. Therefore, co-administration of FARESTON with any of the following medicinal products is contraindicated (also see Contraindications):

- Antiarrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide) or
- Antiarrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide),
- Neuroleptics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride),
- Certain antimicrobial agents (moxifloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine),
- Certain antihistamines (terfenadine, astemizole, mizolastine)
- Others (cisapride, vincamine IV, bepridil, diphemanil).

Drugs which decrease renal calcium excretion, eg. thiazide diuretics, may increase the risk of hypercalcaemia. Enzyme inducers, like phenobarbitone, phenytoin and carbamazepine, may increase the rate of toremifene metabolism thus lowering the steady-state concentration in serum. In such cases doubling of the daily dose may be necessary.

There is a known interaction between anti-oestrogens and warfarin-type anticoagulants leading to a seriously increased bleeding time. Therefore, the concomitant use of toremifene with such medicaments should be avoided.

Theoretically there is a metabolic interaction of toremifene with drugs known to inhibit the CYP 3A4-6 enzyme system. Examples of such drugs are ketoconazole and similar antimycotics, erythromycin, troleandomycin and similar macrolide antibiotics. Concomitant use of those drugs with toremifene should be carefully considered.

ADVERSE REACTIONS

Adverse drug reactions are usually mild. They are mostly due to the hormonal action of toremifene.

The frequency of adverse drug reactions reported in clinical trials or spontaneously is listed below and classified according to body system:

Very common (>10%)	<i>Skin and appendages disorders:</i> hot flushes, sweating
Common (>1%, <10%)	<i>Central and peripheral nervous system disorders:</i> dizziness <i>Gastrointestinal disorders:</i> nausea, vomiting <i>Reproductive disorders:</i> leucorrhoea <i>General disorders:</i> oedema, pain
Uncommon (>0.1%, <1%)	<i>Skin and appendages disorders:</i> pruritus, skin discolouration <i>Central and peripheral nervous system disorders:</i> paresis, tremor, vertigo <i>Vision disorders:</i> reversible corneal verticillata (reversible corneal opacity) <i>Psychic disorders:</i> insomnia <i>Gastrointestinal disorders:</i> constipation <i>Respiratory system disorders:</i> dyspnoea <i>Reproductive disorders:</i> vaginal bleeding <i>General disorders:</i> anorexia, asthenia, back pain, chest pain, fatigue, headache, weight increase
Rare (>0.01%, <0.1%)	<i>Skin and appendages disorders:</i> alopecia, dermatitis <i>Psychic disorders:</i> depression, emotional lability <i>Central and peripheral nervous system disorders:</i> stiffness <i>Hepatic disorders:</i> hepatic enzyme increase, jaundice <i>Metabolic disorders:</i> hypercalcaemia

Thromboembolic events have been reported, although the causal relationship to toremifene treatment remains uncertain.

Treatment was discontinued due to adverse reactions in only about 3% of patients. Most of the cases were due to nausea, vomiting, vertigo, hypercalcaemia and vaginal bleeding. Development of hypercalcaemia in the beginning of the treatment is possible especially in patients with bone metastases.

Endometrial hypertrophy may develop during the treatment due to the hormonal (partial oestrogenic) effect of toremifene. It is unknown whether long-term toremifene use is associated with an increased risk of endometrial carcinoma.

FARESTON increases the QTc interval in a dose related manner (Also see Precautions)

DOSAGE AND ADMINISTRATION

The recommended dose is one tablet (60 mg) daily.

No dose adjustment is needed in renal insufficiency. FARESTON should be used cautiously in patients with hepatic impairment. (see Pharmacokinetics Section, Characteristics in patients).

OVERDOSAGE

No overdose cases are known. Vertigo, headache and dizziness were observed in healthy volunteer studies at a daily dose of 680 mg. The dose-related QTc interval prolongation potential of FARESTON should also be taken into account in cases of overdose. There is no specific antidote and the treatment is symptomatic.

PRESENTATION

Blister Pack containing 30 tablets.

STORAGE

Store below 30°C

POISONS SCHEDULES

Prescription Only Medicine

SPONSOR

Merck Sharp & Dohme (NZ) Ltd
P O Box 99 851
Newmarket
Auckland 1149

Tel: 0800 500 673

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