

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Fareston 60 mg tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 60 mg toremifene (as citrate).

### Excipient with known effect

One tablet contains 28.5 mg of lactose (as monohydrate). For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Tablet.

White, round, flat, bevelled edge tablet with TO 60 on one side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

First line hormone treatment of hormone-dependent metastatic breast cancer in postmenopausal patients.

Fareston is not recommended for patients with estrogen receptor negative tumours.

### **4.2 Posology and method of administration**

#### Posology

The recommended dose is 60 mg daily.

#### *Renal impairment*

No dose adjustment is needed in patients with renal insufficiency.

#### *Hepatic impairment*

Toremifene should be used cautiously in patients with liver impairment (see section 5.2).

#### *Paediatric population*

There is no relevant use of Fareston in the paediatric population.

#### Method of administration

Toremifene is administered orally. Toremifene can be taken with or without food.

### **4.3 Contraindications**

- pre-existing endometrial hyperplasia and severe hepatic failure are contra-indications in long-term use of toremifene
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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 (see also section 4.5).

#### **4.4 Special warnings and precautions for use**

Gynaecological examination should be performed before treatment administration, closely looking at pre-existing endometrial abnormality. Afterwards gynaecological examination should be repeated at least once a year. Patients with additional risk of endometrial cancer, e.g. patients suffering from hypertension or diabetes, having high BMI (> 30) or history of hormone replacement therapy should be closely monitored (see also section 4.8).

Anemia, leukopenia and thrombocytopenia have been reported. Red blood cell, leukocyte or platelet counts should be monitored when using Fareston.

Cases of liver injury, including elevation of liver enzymes (> 10 times upper limit of normal), hepatitis and jaundice have been reported with toremifene. Most of them occurred during the first months of treatment. The pattern of the liver damage was predominantly hepatocellular.

Patients with a history of severe thromboembolic disease should generally not be treated with toremifene (see also section 4.8).

Fareston has been shown to prolong the QTc interval on the electrocardiogram in some patients in a dose-related manner. The following information regarding QT-prolongation is of special importance (for contraindications see section 4.3).

A QT clinical study with a 5-arm parallel design (placebo, moxifloxacin 400 mg, toremifene 20 mg, 80 mg, and 300 mg) has been performed in 250 male patients to characterize the effects of toremifene on the QTc interval duration. The results of this study show a clear positive effect of toremifene in the 80 mg group with mean prolongations of 21–26 ms. Regarding the 20 mg group, this effect is significant as well, according to ICH guidelines, with upper confidence interval of 10–12 ms. These results strongly suggest an important dose-dependent effect. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-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 (incl. Torsade de pointes) and cardiac arrest (see also section 4.3).

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 ms, Fareston should not be used.

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

Hypercalcemia may occur at the beginning of toremifene treatment in patients with bone metastasis and thus these patients should be closely monitored.

There are no systematic data available from patients with labile diabetes, from patients with severely altered performance status or from patients with cardiac failure.

#### Excipients

Fareston tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol (23 mg) sodium per dosage unit, that is to say essentially 'sodium-free'.

### **4.5 Interaction with other medicinal products and other forms of interaction**

An additive effect on QT interval prolongation between Fareston and the following drugs and other medicinal products that may prolong the QTc 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 (see also section 4.3):

- antiarrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- antiarrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- neuroleptics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride)
- certain antimicrobials agents (moxifloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).

Drugs which decrease renal calcium excretion, e.g. thiazide diuretics, may increase the risk of hypercalcaemia.

Enzyme inducers, like phenobarbital, 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-estrogens and warfarin-type anticoagulants leading to a seriously increased bleeding time. Therefore, the concomitant use of toremifene with such drugs should be avoided.

Theoretically the metabolism of toremifene is inhibited by drugs known to inhibit the CYP3A enzyme system which is reported to be responsible for its main metabolic pathways. Examples of such drugs are antifungal imidazoles (ketoconazole); other antifungal agents (itraconazole, voriconazole, posaconazole); protease inhibitors (ritonavir, nelfinavir), macrolides (clarithromycin, erythromycin, telithromycin). Concomitant use of those drugs with toremifene should be carefully considered.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no adequate data from the use of Fareston in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Fareston should not be used during pregnancy.

#### Breast-feeding

In rats, decreased body weight gain of the offspring during lactation was observed.

Fareston should not be used during lactation.

#### Fertility

Toremifene is recommended for postmenopausal patients.

#### 4.7 Effects on ability to drive and use machines

Toremifene has no influence on the ability to drive and use machines.

#### 4.8 Undesirable effects

The most frequent adverse reactions are hot flushes, sweating, uterine bleeding, leukorrhea, fatigue, nausea, rash, itching, dizziness and depression. The reactions are usually mild and mostly due to the hormonal action of toremifene.

The frequencies of the adverse reactions are classified as follows:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $<1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10\,000$  to  $< 1/1\,000$ )

Very rare ( $< 1/10\,000$ ), not known (cannot be estimated from the available data).

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)					Endometrial cancer	
Blood and lymphatic system disorders						Thrombocytopenia, anaemia and leukopenia
Metabolism and nutrition disorders			Loss of appetite			Hypertriglyceridaemia
Psychiatric disorders		Depression	Insomnia			
Nervous system disorders		Dizziness	Headache			
Eye disorders					Transient corneal opacity	
Ear and labyrinth disorders				Vertigo		
Vascular disorders	Hot flushes		Thromboembolic events			
Respiratory, thoracic and mediastinal disorders			Dyspnoea			
Gastrointestinal disorders		Nausea, vomiting	Constipation			
Hepatobiliary disorders				Increase of transaminases	Jaundice	Hepatitis, hepatic

						steatosis
Skin and subcutaneous tissue disorders	Sweating	Rash, itching			Alopecia	
Reproductive system and breast disorders		Uterine bleeding, leukorrhea	Endometrial hypertrophy	Endometrial polyps	Endometrial hyperplasia	
General disorders and administration site conditions		Fatigue, oedema	Weight increase			

Thromboembolic events include deep venous thrombosis, thrombophlebitis and pulmonary embolism (see also section 4.4).

Toremifene treatment has been associated with changes in liver enzyme levels (increases of transaminases) and in very rare occasions with more severe liver function abnormalities (jaundice).

A few cases of hypercalcaemia have been reported in patients with bone metastases at the beginning of toremifene treatment.

Endometrial hypertrophy may develop during the treatment due to the partial estrogenic effect of toremifene. There is a risk of increased endometrial changes including hyperplasia, polyps and cancer. This may be due to the underlying mechanism/estrogenic stimulation (see also section 4.4). Fareston increases the QT interval in a dose-related manner (see also section 4.4).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in [Appendix V](#)**.

## **4.9 Overdose**

Vertigo, headache and dizziness were observed in healthy volunteer studies at 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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Endocrine therapy, Anti-estrogens, ATC code: L02BA02

Toremifene is a nonsteroidal triphenylethylene derivative. As other members of this class, e.g. tamoxifen and clomifene, toremifene binds to estrogen receptors and may produce estrogenic, anti-estrogenic or both effects, depending upon the duration of treatment, animal species, gender, target organ and variable selected. In general, however, nonsteroidal triphenylethylene derivatives are predominantly anti-estrogenic in rats and man and estrogenic in mice.

In post-menopausal breast cancer patients, toremifene treatment is associated with modest reductions in both total serum cholesterol and low density lipoprotein (LDL).

Toremifene binds specifically to estrogen receptors, competitively with oestradiol, and inhibits estrogen-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 estrogen-dependent.

The anti-tumour effect of toremifene in breast cancer is mainly due to the anti-estrogenic 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.

## **5.2 Pharmacokinetic properties**

### Absorption

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.

### Distribution

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 intravenous study. Toremifene binds extensively (> 99.5%) to serum proteins, mainly to albumin. Toremifene obeys linear serum kinetics at oral daily doses between 11 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 per day.

### Biotransformation

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 twice compared to those of the parent compound. It has similar anti-estrogenic, albeit weaker anti-tumour activity than the parent compound.

It is bound to plasma proteins even more extensively than toremifene, the protein bound fraction being > 99.9%. 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 concentrations during toremifene treatment are too low to have any major biological importance.

### Elimination

Toremifene is eliminated mainly as metabolites to the faeces. Enterohepatic circulation 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 concentrations have no positive correlation at the recommended daily dose of 60 mg.

No information is available concerning polymorphic metabolism. 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 CYP3A.

Pharmacokinetics of toremifene were investigated in an open study with four parallel groups of ten subjects: normal subjects, patients with impaired (mean AST 57 U/L - mean ALT 76 U/L - mean gamma GT 329 U/L) or activated liver function (mean AST 25 U/L - mean ALT 30 U/L - mean gamma GT 91 U/L - patients treated with antiepileptics) and patients with impaired renal function (creatinine: 176 µmol/L). In this study the kinetics of toremifene in patients with impaired renal function were not significantly altered as compared to normal subjects. The elimination of toremifene

and its metabolites was significantly increased in patients with activated liver function and decreased in patients with impaired liver function.

### **5.3 Preclinical safety data**

The acute toxicity of toremifene is low with LD-50 in rats and mice of more than 2 000 mg/kg. In repeated toxicity studies the cause of death in rats is gastric dilatation. In the acute and chronic toxicity studies most of the findings are related to the hormonal effects of toremifene. The other findings are not toxicologically significant. Toremifene has not shown any genotoxicity and has not been found to be carcinogenic in rats. In mice, estrogens induce ovarian and testicular tumours as well as hyperostosis and osteosarcomas. Toremifene has a species-specific estrogen-like effect in mice and causes similar tumours. These findings are postulated to be of little relevance for the safety in man, where toremifene acts mainly as an anti-estrogen.

Non clinical *in vitro* and *in vivo* studies have evidenced the potential of toremifene and its metabolite to prolong cardiac repolarisation and this can be attributed to the blockade of hERG channels.

*In vivo*, high plasma concentrations in monkeys caused a 24% prolongation in QTc, which is in line with QTc findings in humans.

It is also to be noted that the C<sub>max</sub> observed in the monkeys (1 800 ng/ml) is two-fold compared to the mean C<sub>max</sub> observed in humans at a daily dose of 60 mg.

Action potential studies in isolated rabbit heart have shown that toremifene induce cardiac electrophysiological changes which start to develop at concentrations approximately 10 fold compared to the calculated free therapeutic plasma concentration in human.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Maize starch  
Lactose monohydrate  
Povidone  
Sodium starch glycolate  
Magnesium stearate  
Cellulose, microcrystalline  
Silica, colloidal anhydrous.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Green PVC foil and aluminium foil blister in a cardboard box.



Package sizes: 30 and 100 tablets.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### **7. MARKETING AUTHORISATION HOLDER**

Orion Corporation  
Orionintie 1  
FI-02200 Espoo  
Finland

### **8. MARKETING AUTHORISATION NUMBERS**

EU/1/96/004/001  
EU/1/96/004/002

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 14 February 1996  
Date of latest renewal: 2 February 2006

### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Orion Corporation Orion Pharma  
Joensuunkatu 7  
FI-24100 Salo  
Finland

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

Not applicable.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Fareston 60 mg tablets

toremifene

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 tablet contains: 60 mg toremifene (as citrate)

**3. LIST OF EXCIPIENTS**

lactose monohydrate

**4. PHARMACEUTICAL FORM AND CONTENTS**

tablet

30 tablets

100 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Orion Corporation  
Orionintie 1  
FI-02200 Espoo  
Finland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/96/004/001 30 tablets  
EU/1/96/004/002 100 tablets

**13. BATCH NUMBER**

Batch:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

fareston 60 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC: {number}  
SN: {number}  
NN: {number}, if applicable nationally

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
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<b>BLISTER</b>
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<b>1. NAME OF THE MEDICINAL PRODUCT</b>
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Fareston 60 mg tablets

toremifene

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
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Orion Corporation

<b>3. EXPIRY DATE</b>
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EXP:

<b>4. BATCH NUMBER</b>
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Batch:

<b>5. OTHER</b>
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## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **Fareston 60 mg tablets** toremifene

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Fareston is and what it is used for
2. What you need to know before you take Fareston
3. How to take Fareston
4. Possible side effects
5. How to store Fareston
6. Contents of the pack and other information

#### **1. What Fareston is and what it is used for**

Fareston contains the active substance toremifene, an anti-estrogen. Fareston is used for the treatment of a certain type of breast tumour in women who have had their menopause.

#### **2. What you need to know before you take Fareston**

##### **Do not take Fareston**

- if you are allergic to toremifene or any of the other ingredients of this medicine (listed in section 6)
- if you have a thickening of the womb lining
- if you have severe liver problems
- if you were born with or have had any condition which causes certain abnormal changes in the electrical recording of the heart (electrocardiogram or ECG)
- if you have a salt imbalance in the blood, especially low concentrations of potassium in the blood (hypokalaemia) which are currently not corrected by treatment
- if you have a very slow heart rate (bradycardia)
- if you have a heart failure
- if you have a history of abnormal heart rhythms (arrhythmias)
- if you are taking other medicines that may affect your heart (see section 2 Other medicines and Fareston).

This is because Fareston can affect your heart by delaying the conduction of electrical signals within your heart (prolongation of QT-interval).

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Fareston:

- if you have unstable diabetes
- if your general well-being is severely deteriorated
- if you have previously had a condition in which blood clots formed in blood vessels, for example in your lungs (lung embolism) or in the veins of your legs (deep vein thrombosis)

- if you experience an abnormal heart rhythm whilst taking Fareston. Your doctor may advise you to stop taking Fareston and perform a medical test to see how your heart is working (ECG) (see section 2 Do not take Fareston).
- if you have any heart condition, including chest pain (angina)
- if your cancer has spread to the bones (bone metastasis) as calcium blood levels may increase at the beginning of treatment with Fareston. Your doctor will conduct regular medical check-ups.
- if you have been told by your doctor that you have an intolerance to certain sugars, like lactose (see section 2 Fareston contains lactose).

You should have gynaecological examinations before you start treatment with Fareston and at least once a year following the start of treatment with Fareston. Your doctor will conduct regular medical check-ups if you have high blood pressure, diabetes, have taken hormone replacement therapy or if you are obese (BMI over 30).

### **Other medicines and Fareston**

Tell your doctor if you are taking, have recently taken or might take any other medicines. The dose of some of these may have to be adjusted while you are on Fareston. In particular please tell your doctor if you are taking any of the following:

- water tablets (diuretics of thiazide type)
- medicines to prevent blood clotting such as warfarin
- medicines used to treat epilepsy such as carbamazepine, phenytoin, phenobarbital
- medicines used to treat fungal infections such as ketoconazole, itraconazole, voriconazole, posaconazole
- medicines used to treat bacterial infections (antibiotics) such as erythromycin, clarithromycin and telithromycin
- medicines used to treat viral infection such as ritonavir and nelfinavir.

Do not take Fareston together with the following medicines as there is an increased risk that your heartbeat may be altered (see section 2 Do not take Fareston):

- medicines used to treat abnormal heart rhythm (antiarrhythmics); such as quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide and ibutilide
- medicines used to treat mental and behavioral disorders (neuroleptics); such as phenothiazines, pimozide, sertindole, haloperidol and sultopride
- medicines used to treat infections (antimicrobials); such as moxifloxacin, erythromycin (infusion) pentamidine and antimalarials (particularly halofantrine)
- certain medicines to treat allergies; such as terfenadine, astemizole and mizolastine
- others; cisapride, intravenous vincamine, bepridil, diphemanil.

If you are admitted to the hospital or if you are prescribed a new medicine, please tell your doctor that you are taking Fareston.

### **Pregnancy and breast-feeding**

Do not use Fareston during pregnancy or breast feeding.

### **Driving and using machines**

Fareston has no influence on the ability to drive and use machines.

### **Fareston contains lactose**

Fareston contains 28.5 mg lactose (as monohydrate) per tablet. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

### **Other excipients**

This medicine contains less than 1 mmol (23 mg) sodium per tablet that is to say essentially 'sodium-free'.

### 3. How to take Fareston

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The usual dose is one 60 mg tablet taken orally, once daily. Fareston can be taken with or without food.

#### **If you take more Fareston than you should**

Contact your doctor, pharmacist or the nearest hospital immediately. Symptoms of overdose may be dizziness and headache.

#### **If you forget to take Fareston**

If you miss one dose take the next tablet as usual and continue treatment as recommended. Do not take a double dose to make up for a forgotten tablet. If you have missed several doses, please inform your doctor and follow his instructions.

#### **If you stop taking Fareston**

The treatment with Fareston should only be stopped when advised by your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people):

- hot flushes, sweating.

Common (may affect up to 1 in 10 people):

- fatigue, dizziness, depression
- nausea (feeling sick), vomiting
- rash, itching, oedema (swelling)
- uterine bleeding, white discharge.

Uncommon (may affect up to 1 in 100 people):

- headache, sleep disorders
- weight increase, constipation, loss of appetite
- thickening of the lining of the womb (endometrial hypertrophy)
- blood clot for example in the lung (thromboembolic events)
- shortness of breath.

Rare (may affect up to 1 in 1 000 people):

- a feeling of spinning (vertigo)
- growth on the lining of the womb (endometrial polyps)
- increase in liver enzymes (increase of liver transaminases).

Very rare (may affect up to 1 in 10 000 people):

- changes in the lining of the uterus (endometrium), cancer of the lining of the womb (endometrial cancer)
- hair loss (alopecia)
- cloudiness of the eye surface (transient corneal opacity)
- yellowing of the skin or whites of the eyes (jaundice).

Not known (frequency cannot be estimated from the available data):

- low number of white blood cells, which are important in fighting infection (leukopenia)
- low number of red blood cells (anaemia)

- low number of platelets (thrombocytopenia)
- inflammation of the liver (hepatitis)
- high blood levels of triglycerides, a type of fat.

You should contact your doctor immediately if you notice any of the following:

- swelling or tenderness in your calf
- unexplained shortness of breath or sudden chest pain
- vaginal bleeding or changes in vaginal discharge.

Fareston causes certain abnormal changes in the electrical recording of the heart (electrocardiogram or ECG). See section 2 Warnings and precautions.

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Fareston**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Fareston contains**

- The active substance is toremifene; each tablet contains 60 mg (as citrate).
- The other ingredients are maize starch, lactose monohydrate, povidone, sodium starch glycolate, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

### **What Fareston looks like and contents of the pack**

White, round, flat, bevelled edge tablet with TO 60 on one side.  
30 and 100 tablets. Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Orion Corporation  
Orionintie 1  
FI-02200 Espoo  
Finland

### **Manufacturer**

Orion Corporation Orion Pharma  
Joensuunkatu 7  
FI-24100 Salo  
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Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

#### **ANNEX IV**

#### **SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)**



## **Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for toremifene, the scientific conclusions of PRAC are as follows:

In view of available data on hypertriglyceridaemia from the literature and spontaneous cases including some cases with a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between toremifene and hypertriglyceridaemia is at least a reasonable possibility. The PRAC concluded that the product information of products containing torefemifene should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

## **Grounds for the variation to the terms of the Marketing Authorisation(s)**

On the basis of the scientific conclusions for toremifene the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing toremifene is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.