ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS
1. TRADE NAME OF THE PRODUCT

FARESTON® (Toremifene)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Toremifene 60 mg (as toremifene citrate)
Inactive ingredients: Maize starch, lactose, povidone, sodium starch glycolate, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate.

3. PHARMACEUTICAL FORM

Tablet for oral administration

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 oestrogen receptor negative tumours.

4.2 Posology and method of administration

The recommended dose is 60 mg, one tablet, daily.

No dose adjustment is needed in renal insufficiency. Toremifene should be used cautiously in patients with hepatic impairment (see also section 5.2. Pharmacokinetic properties, b) Characteristics in patients).

4.3 Contra-indications

Pre-existing endometrial hyperplasia and severe hepatic failure are contra-indications in long-term use of toremifene.

4.4 Special warnings and special precautions for use

Experience of the long-term use (more than one year) of toremifene is limited.

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

Because hypercalcaemia may occur at the beginning of the treatment patients with bone metastases should also be closely monitored.

There is no data on the bone effect of toremifene.

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

There is 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.
4.5 Interaction with other medicaments and other forms of interaction

No specific interaction studies have been performed.

Drugs which decrease renal calcium excretion, e.g. thiazide diuretics, may increase the risk of hypercalcaemia. Enzyme inductors, 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-oestrogens 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 CYP 3A4-6 enzyme system which is reported to be responsible for its main metabolic pathways. Examples of such drugs are ketoconazole and similar antimycotics, erythromycin and troleandomycin. Concomitant use of those drugs with toremifene should be carefully considered.

4.6 Pregnancy and lactation

Toremifene is recommended for postmenopausal patients. Owing to the lack of specific data in humans toremifene should not be used during pregnancy and lactation.

In the animal reproduction studies toremifene has been shown to prevent implantation, to induce parturition failures, and to reduce perinatal survival. In addition, treatment during organogenesis induces changes in ossification, rib abnormalities, and oedematous foetuses.

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

4.7 Effects on ability to drive and use machines

None

4.8 Undesirable effects

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

In clinical studies, the most frequent adverse reaction is hot flushes (up to 20%). Other common adverse reactions include sweating (14 %), nausea (8 %), leucorrhea (8 %), dizziness (4%), oedema (3 %), pain (2 %) and vomiting (2 %).

Less frequent adverse reactions (frequency < 1%) include vaginal bleeding, chest pain, fatigue, back pain, headache, skin discoloration, weight increase, insomnia, constipation, dyspnea, paresis, tremor, vertigo, pruritus, anorexia, reversible cornea verticillata (reversible corneal opacity) and asthenia. Thromboembolic events have been reported, although the causal relationship to toremifene treatment remains conjectural.

Rare adverse reactions with unclear causal relationship to toremifene include dermatitis, alopecia, emotional lability, depression, jaundice and stiffness.

Treatment was discontinued due to adverse reactions in 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 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/oestrogenic stimulation.

4.9 Overdose

No overdose cases are known.

Vertigo, headache and dizziness were observed in healthy volunteer studies at daily dose of 680 mg. There is no specific antidote and the treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Toremifene is a nonsteroidal triphenylethylene derivative. As other members of this class, e.g. tamoxifen and clomifene, toremifene binds to oestrogen receptors and may produce oestrogenic or anti-oestrogenic, 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-oestrogenic in rats and man and oestrogenic in mice.

In female rats the lowest dose of toremifene that produces an intrinsic oestrogenic effect on the uterus is about 40 times higher than that of tamoxifen. In the same model the minimum 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 is 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.

5.2 Pharmacokinetic properties

a) 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 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.

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-oestrogenic, 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.

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.

b) Characteristics in patients

Clinical antitumour 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 CYP 3A4/3A5.

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 2000 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, 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 man, where toremifene acts mainly as an anti-oestrogen.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Maize starch
Lactose
Povidone
Purified water
Sodium starch glycolate
Magnesium stearate
Microcrystalline cellulose
Colloidal anhydrous silica

6.2 Incompatibilities
None.

6.3 Shelf life
5 years between +15 - +30 °C.

6.4 Special precautions for storage
None.

6.5 Nature and contents of container
Green PVC foil and aluminium foil blister in a cardboard box.
Package sizes: 30 and 100 tablets.

6.6 Instructions for use/handling
None
7. HOLDER OF THE MARKETING AUTHORISATION

ERCOFHARM A/S
Bøgeskovvej 9
DK-3490 KVISTGÅRD
Denmark

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE REVISION OF THE TEXT

ANNEX II
MANUFACTURING AUTHORISATION AND CONDITIONS OF THE MARKETING AUTHORISATION
A. -HOLDER(S) OF THE MANUFACTURING AUTHORISATION(S)

Manufacturer of the active ingredient: Orion Corporation Fermion Oulu Plant, Laaketehtaankatu 2, 90650 Oulu, Finland.

Manufacturer of finished product and responsible for batch release in the European Union: Orion Corporation Orion-Farmos Turku Plant Tengstrominkatu 6-8, 20360 Turku, Finland.
GMP certificate issued by the Finnish Authority on November 1994.

B. - CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
(Articles 2 and 3 of Directive 92/26/EEC )

Medicinal product subject to non-renewable medical prescription.

C. - SPECIFIC OBLIGATIONS OF THE MARKETING AUTHORISATION HOLDER
( Post-authorisation commitments )

The company, after having been consulted (CPMP/502/95), will meet the commitment to submit the results of the additional studies set out below and detailed in the Assessment Report (CPMP/453/95 Chapter II point 3) attached to this opinion. The results of those studies should be submitted within the defined timeframe to the EMEA after the marketing authorisation is granted.

1. Residual data on the validation of the HPLC Assay for active substance will be submitted on 15 December 1995.

2. The stability of the active substance should be re-assessed. The study will start on 15 October 1995 and the results submitted on an ongoing basis every six months. The final report will be submitted on 31 October 2000.

3. Additional dissolution test will be performed and the results submitted on 31 March 1996.

4. Additional clinical information on the gynaecological follow up (including endometrial biopsy) will be submitted on 31st December 1999 (Studies 3008009 and 3008011).

5. Additional clinical information on the effect of Toremifen on bone mineralization will be provided on 31st December 1998 (study 092B06/092B11).
ANNEX III
LABELLING AND USER PACKAGE LEAFLET
A. LABELLING
NAME OF THE MEDICINAL PRODUCT followed by the COMMON NAME

FARESTON® (toremifene)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Toremifene citrate, corresponding to toremifene : 60 mg per tablet
Excipients q.s. 1 tablet, including lactose

PHARMACEUTICAL FORM AND CONTENTS BY UNIT

Boxes of / 30 and 100 tablets of 60 mg each

LIST OF EXCIPIENTS KNOWN TO HAVE A RECOGNISED ACTION OR EFFECT

Lactose

METHOD AND ROUTE OF ADMINISTRATION

Oral administration

LEGAL STATUS

MEDICINAL PRODUCT SUBJECT TO MEDICAL PRESCRIPTION

SPECIAL WARNING

THIS MEDICINAL PRODUCT MUST BE KEPT OUT OF REACH OF CHILDREN

EXPIRY DATE

(month/year)

SPECIAL STORAGE PRECAUTIONS

Not applicable

SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTED MATERIALS DERIVED FROM SUCH PRODUCTS

No special precautions

NAME AND ADDRESS OF THE HOLDER OF THE MARKETING AUTHORIZATION

ERCOPHARM A/S
Bøgeskovvej 9
DK-3490 KVISTGÅRD
Denmark

NUMBER OF THE MARKETING AUTHORIZATION
MANUFACTURER'S BATCH NUMBER

BLISTER PACK

NAME OF THE MEDICINAL PRODUCT followed by the COMMON NAME
FARESTON® (toremifene)

NAME OF THE MARKETING AUTHORIZATION HOLDER
ERCOPHARM A/S

EXPIRY DATE

BATCH NUMBER
B.-USER PACKAGE LEAFLET
Please read this leaflet carefully before you start to take your medicine. This leaflet provides a summary of the information known about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

Remember this medicine is for you. Only a doctor can prescribe this medicine and it may harm someone else, even if their symptoms are the same as yours.

1. IDENTIFICATION OF THE MEDICINAL PRODUCT

Name of the medicinal product

FARESTON® (Toremifene)

Composition

Active ingredient: Toremifene 60 mg (as toremifene citrate)
Inactive ingredients: Maize starch, lactose, povidone, sodium starch glycolate, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate.

Pharmaceutical form

Tablets containing 60 mg of toremifene.
Boxes of 30 and 100 tablets.

Pharmacological group

Fareston® is an anti-oestrogen.

Marketing authorization holder

ERCOPHARM A/S
Bøgeskovvej 9
DK-3490 KVISTGAARD
DENMARK

Manufacturer

ORION Corporation
Tengströmininkatu 6-8
FIN-20360 TURKU
FINLAND

2. WHAT YOUR MEDICINE IS USED FOR (THERAPEUTIC INDICATIONS)

Fareston® is used for the treatment of a certain type of breast tumor in women who have had their menopause.
3. INFORMATION NECESSARY BEFORE TAKING THE MEDICINAL PRODUCT

When you should not take this medicine (Contra-indications)

Patients who already have a thickening of the womb lining or severe liver problems should not take Fareston® as long-term therapy. If you feel this applies to you contact your doctor.

Special precautions

Fareston® should be used with caution in patients with heart failure (including angina pectoris), in patients having bone disorders since hypercalcemia (increased concentration of calcium in the blood) may occur at the beginning of the treatment, in diabetics and in patients with poor physical condition. Patients with a history of severe problem of blood clotting should generally not take Fareston®. If you feel this applies to you contact your doctor or pharmacist.

Keep out of the reach of children.

Interactions with other medicinal products and other forms of interaction

Your doctor should be informed about all other medicines you are taking, because the dose of some may have to be adjusted while being treated with Fareston®.

These include: diuretics (water tablets) of thiazide type, anticoagulants (to prevent blood clotting) of warfarin type, certain anti-epileptics (medicines used to treat epilepsy e.g. carbamazepine, phenytoin, phenobarbital), certain anti-mycotics (used to treat fungal infections such as ketoconazole) and certain antibiotics (such as erythromycin and troleandomycin).

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

Use during pregnancy and breastfeeding

Fareston® is recommended for women who have had their menopause. It should not be used during pregnancy and breastfeeding.

Effects on ability to drive and use machinery

None

4. INSTRUCTIONS FOR USE

Dosage
The recommended dose is 60 mg, one tablet daily.

Method and route of administration
The tablet is taken orally.
**Frequency of administration**
One tablet once a day.

**Duration of treatment**
Life-long treatment or as instructed by your doctor.

**Actions to be taken in case of overdose**
In case of accidental overdose, contact your doctor immediately.

**Action to be taken when one or more doses have not been taken**
Daily intake is recommended.
If you miss one dose take the next tablet as usual and continue treatment as recommended. If you have missed several doses, please inform your doctor and follow his instructions.

5. **UNWANTED EFFECTS**
Along with its desired effects, a medicine may cause some undesirable effects.

The undesirable effects that are most likely to occur are: hot flushes, sweating, leucorrhea (discharge of white fluid from the vagina), nausea (feeling sick), dizziness, swelling, pain and vomiting.

Other effects are: vaginal bleeding, chest pain, tiredness, back pain, headache, skin discoloration, weight increase, insomnia (inability to sleep), constipation, shortness of breath, paresis (inability to move), tremor (shaking), itching, anorexia (loss of appetite or weight), reversible sight problems and weakness.

If any other effect is noticed you should tell your doctor or pharmacist about it.

6. **EXPIRY DATE**
Do not use the product after the expiry date on the package.

Storage: the product should be stored between 15 and 30°C.

7. **LATEST REVISION OF THIS DOCUMENT**