

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 30 November 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Toremifene is an anti-oestrogenic agent chemically derived from tamoxifen.

Tamoxifen has been the standard therapy for breast cancer in post-menopausal women for the last 20 years. Toremifene as an anticancer agent is comparable to tamoxifen with respect to activity and toxicity.

There is no human clinical data to support that toremifene has a superior safety profile compared with tamoxifen.

Clinical data for the claimed lower oestrogenic activity of toremifene are insufficient.

Whether toremifene has greater osteoporotic effect than tamoxifen with long-term use can only be assessed when data from adjuvant and prophylactic trials become available.

Substantial discussion took place on the efficacy of toremifene with respect to the oestrogen receptor status of the patient.

The CPMP agreed that on the basis of the available data, the clinical efficacy of toremifene is proven in these patients having oestrogen receptor positive breast tumour.

2. Chemical, pharmaceutical, and biological aspects

The chemical and pharmaceutical assessment of Fareston has been considered satisfactory. The European Drug Master File was submitted and considered acceptable.

3. Toxicopharmacological aspects

Pharmacodynamics

Toremifene, like tamoxifen binds to oestrogen receptors and may exert oestrogenic effects or anti-oestrogenic effects, or both, depending on the experimental conditions.

Toremifene has *in vitro* antitumour properties in oestrogen receptor positive line cells (MCF-7 and ZR 75.1).

When tested on tamoxifen resistant human MDA-MB-231 cells, transplanted into athymic mice, toremifene had no anti-tumour effect.

Based on the data, effects of toremifene and tamoxifen on cell cycle kinetics and oncogenes are comparable.

Other general pharmacological effects of toremifene are few, mild and transient.

Pharmacokinetics

The pharmacokinetics of toremifene have been investigated in detail after single and multiple oral doses in mice, rats, dogs and monkeys.

The absorption of toremifene is complete.

Toremifene is distributed to almost all tissues, including target tissue (tumour).

The metabolism of toremifene is complex, and several metabolites have toremifene-like effects. Induction of cytochrome P450 occurs.

Excretion takes place via biliary excretion and enterohepatic circulation. Final excretion route is via faeces with minimal amounts excreted via urine.

Toremifene did not interact with antipyrine elimination in isolated perfused rat liver.

Toxicology

Acute and chronic toxicity studies have shown that most of the observed findings were related to the hormonal effects of toremifene.

Toremifene is devoid of mutagenic or clastogenic activity: an additional study on mutagenic potential of toremifene in eukaryotic cell confirmed the absence of such an activity; the company provided a preliminary report in October 1995 and the full report circulated in December 1995.

In rats, toremifene does not have carcinogenic effects. It does not cause DNA-adducts formation, hepatocellular carcinoma or endometrial neoplasia.

In mice, the observed carcinogenicity (testis, ovaries, bone) of toremifene is expected from its pharmacodynamic effects. Its relevance to clinical use appears low due to the fact that toremifene acts mainly as an anti-oestrogen in man.

In summary, Part III of the dossier submitted was considered adequate to describe and assess the pharmaco-toxicological potential of toremifene.

4. Clinical aspects

Toremifene (60 mg/day) is an anti-oestrogen with an efficacy profile comparable to that of tamoxifen (20 mg/day) in post-menopausal women with disseminated breast cancer.

It is, at present, unknown if toremifene therapy, as compared to tamoxifen therapy, will have significant clinical advantages in post-menopausal women with advanced breast cancer.

Human Pharmacology

27 phase I studies were conducted on a total of 725 women to determine the pharmacological profile and tolerability of toremifene. In healthy post-menopausal volunteers it was shown that toremifene 20 mg or more, daily, exerted an anti-oestrogenic effect (vaginal cornification assay in oestrogen primed vaginal epithelium).

Clinical Pharmacology

Pharmacodynamics

In post-menopausal women with advanced breast cancer (18 phase II studies involving 1037 women) it was shown that toremifene 60 mg/day increased the duration of response significantly in patients with oestrogen receptor concentrations over 50 fmol/mg protein. The beneficial effect of increasing the daily dose of toremifene above 60 mg is marginal (maximally 300 mg daily). There were no clinically significant changes in haematological blood chemistry or vital signs either with toremifene or tamoxifen in controlled phase I-II clinical trials. No unusual adverse reactions were seen in women receiving toremifene.

Pharmacokinetics

The pharmacokinetics of orally given toremifene has been studied after single and repeated administration in healthy volunteers and breast cancer patients (n= 329 in 14 studies). A sensitive and reliable HPLC-method was used for detection of toremifene and its metabolites in serum or plasma.

Toremifene is rapidly and well absorbed after oral administration and obeys linear serum kinetics at oral doses between 11 and 680 mg. Toremifene serum kinetics followed the two-compartment model, with a mean distribution half-life of 4-5 days. As a consequence of the slow elimination, the time to reach steady-state plasma concentrations was between 1 and 6 weeks.

The absolute bioavailability of toremifene has not been calculated due to lack of data obtained with intravenous toremifene (poor solubility of toremifene in water).

Toremifene is extensively metabolised, mainly in the liver. The main metabolite in serum is N-dimethyl-toremifene, the half life of which is 11 days.

The pharmacokinetics of toremifene has been described satisfactorily in at-risk patients (women with liver and renal insufficiency and women treated with liver enzyme inducers).

Clinical experience

Phase III studies including a total of 1869 post-menopausal women with advanced metastatic or disseminated breast cancer. Three studies, considered as pivotal studies by the applicant, compared

toremifene 40-240 mg daily with tamoxifen 20-40 mg daily in prospective randomised trials (5/044, 5/049, 5/050).

Study 5/044 was a multicentre open randomised trial. This large clinical trial enrolled 648 post-menopausal women who had never received chemotherapy or hormonal therapy for dissemination. The endpoints studied were rate of response, median time to progression, median survival time and median overall survival.

It may be criticised that the trial was not blinded. However, the data presented strongly suggests that toremifene 60 mg daily is clinically equivalent to tamoxifen 20 mg daily as palliative therapy in post-menopausal women with advanced breast cancer. No additional beneficial effect was obtained by increasing the daily dose of toremifene to 200 mg. No unexpected adverse reactions were detected in the treatment groups.

Study 5/049 was a double-blind multicentre study. A total of 415 post-menopausal women with metastatic breast cancer (Oestrogen receptor positive or oestrogen receptor unknown inoperable primary metastatic or recurrent mammary cancer) were randomised to receive tamoxifen 40 mg daily (n = 201, 184 eligible) or toremifene 60 mg daily (n = 214, 195 eligible). The treatment was given at least 8 weeks or until progression or severe toxicity.

The clinical trial gave evidence of the clinical efficacy of toremifene 60 mg daily in postmenopausal women with metastatic breast cancer. The safety profile of toremifene is comparable to that of tamoxifen.

Study 5/050 was a multi-centre open randomised trial including 463 post-menopausal women with advanced breast cancer. Treatment consisted of tamoxifen 40 mg daily (n = 149, 128 evaluable), toremifene 60 mg daily (n= 157, 126 evaluable) or toremifene 240 mg daily (n= 154, 139 evaluable) for at least 8 weeks or until tumour progression or drug related toxicity.

Response rate, progression free interval and overall survival were the main end points considered.

The efficacy profile of toremifene 60 mg/day was comparable to that of tamoxifen 40 mg/day. The benefit/risk ratio was not significantly improved by increasing the toremifene dose to 240 mg/day.

Study 5/055

In this study the efficacy and tolerability of toremifene 40 mg could not be distinguished from those of tamoxifen 20 mg.

Analysis related to hormonal receptor status

For the studies 5/044, 5/049 and 5/050, a pooled analysis of the two subsets of the patients (Oestrogen receptor positive and oestrogen receptor status unknown) including the three primary efficacy criteria, response rate, time to progression and survival has been submitted (Table 1). In these studies, patients with known oestrogen receptor negative tumours were excluded.

For the patients with estrogen receptor positive tumours, the criteria for therapeutic equivalence were met for each primary efficacy criteria.

In the subsets of patients with unknown oestrogen receptor status, in one study (study 5/049) the criteria for equivalence were met for response rate and survival, but not for time to progression. In the pooled analysis of all three studies no statistical difference could be seen in this subset of patients.

The pooled analysis including all patients (oestrogen receptor positive and oestrogen receptor unknown) showed equivalent efficacy between toremifene and tamoxifen in each primary efficacy criteria.

Regarding particularly oestrogen receptor negative patients, two small clinical trials in which this subset of patients was included showed no responders.

Meta-analysis of the pivotal Phase III studies

A meta-analysis performed on five studies has confirmed the equivalence of tamoxifen 20 mg and toremifene 60 mg in terms of efficacy.

Concerning the tolerability, toremifene 60 mg could not be distinguished from that of tamoxifen 20 mg.

The adverse reactions were usually mild and transient. Except for the expected anti-oestrogenic activity, no signs of systemic toxicity were observed.

Clinical laboratory parameters (haematology, liver function, renal function, electrolytes) were for the majority of patients within the normal range, except occasional increases in liver transaminase concentrations and hypercalcaemia in patients with bone metastases.

The long-term toxicity could not be evaluated in the currently available studies.

It is still unknown if toremifene will differ from tamoxifen with respect to incidence of endometrial cancer and bone mineralisation in treated women.

**TABLE 1: Toremifene 60 vs. tamoxifen 20/40
Meta-analysis of studies 05/044, 05/049 and 05/050**

	ER Positive Patients ¹	ER Unknown Patients ²	All patients ³
Response Rate Difference (toremifene : tamoxifen)	-3.4%	2.5%	-0.8%
90% Confidence Interval ⁴	-9.0% to 2.1%	-3.2% to 8.3%	-4.8% to 3.2%
P-value	0.312	0.469	0.744
Time to Progression			
Hazard Ratio (toremifene : tamoxifen)	0.93	0.87	0.91
90% Confidence Interval ⁵	0.80 to 1.08	0.74 to 1.06	0.81 to 1.02
P-value	0.407	0.267	0.158
Overall Survival			
Hazard Ratio (toremifene : tamoxifen)	1.06	0.86	1.00
90% Confidence Interval ⁵	0.97 to 1.29	0.67 to 1.09	0.86 to 1.16
P-value	0.651	0.294	0.966

¹ Number of patients : 318 (tamoxifen) and 335 (toremifene)
² Number of patients : 247 (tamoxifen) and 257 (toremifene)
³ Number of patients : 565 (tamoxifen) and 592 (toremifene)
⁴ Equivalence criteria, lower limit 10%
⁵ Equivalence criteria, lower limit 0.80

Post Marketing experience

Toremifene has been marketed since 1988 in Finland. Two adverse events (one with acute hypercalcaemia and one with hepatic cytolysis) had been reported during high-dose (200-240 mg daily) toremifene treatment at the time of the CPMP Opinion.

Since then more experience has been gained. With regard to thrombo-embolic complications 25 cumulative cases were reported possibly related to toremifene treatment. Also some cases of elevation of transaminases have been reported.

In the meantime two studies have been published. They show that in post-menopausal toremifene treatment is associated with modest reductions in both total serum cholesterol and low density lipoprotein (LDL).

5. Conclusions

Toremifene is a new non-steroidal triphenylethylene derivative with anti-oestrogenic activity developed for the treatment of oestrogen dependent cancers, especially breast cancer. Like the triphenylethylene analogue tamoxifen, toremifene binds specifically to oestrogen receptor, thereby blocking some of the oestrogen mediated growth stimuli of mammary tumour cells.

The chemical and pharmaceutical documentation and the preclinical experience were considered by the CPMP as satisfactory.

In three large clinical trials a clinically significant palliative effect has been documented in post-menopausal women with disseminated breast cancer during toremifene (60 mg/day) treatment. The effect is comparable to that obtained during tamoxifen (20-40 mg/day) treatment.

Most of the observed adverse events during toremifene therapy were transient and mostly due to the hormonal effects of the compound. Increases in liver enzymes and hypercalcaemia can be seen in patients with liver and bone metastases.

Data are insufficient to allow evaluation of the long-term toxicity of toremifene, and it is still unknown if toremifene will differ from tamoxifen with respect to incidence of endometrial cancer and bone mineralisation in treated women.

There are no data to support an effect for toremifene in pre-menopausal women with advanced breast cancer or in post-menopausal women with localised disease.

It has not been documented that toremifene at higher doses can be used as second-line treatment of mammary carcinomas after failure of other hormonal or cytotoxic treatments.

The available data suggest that the benefit/risk ratio of toremifene is comparable to that of tamoxifen in post-menopausal women with disseminated breast cancer oestrogen receptor positive.

In the three pivotal studies patients who were found oestrogen receptor negative were excluded. Two small clinical trials in which oestrogen receptor negative patients were included showed no responders.

On the basis of these findings the CPMP in its September 1995 meeting had a substantial discussion on the indication of Fareston and it was agreed that Fareston is not recommended for patients with oestrogen receptor negative tumours.

The indication is the following:

“First line hormone treatment of hormone-dependent metastatic breast cancer in post-menopausal patients. Fareston is not recommended for patients with oestrogen receptor negative tumours”.