Eikenhatsu 3046
27 October 2000

To: Director of the Pharmaceutical and Medical Safety Bureau

Director of the National Institute of Health Sciences

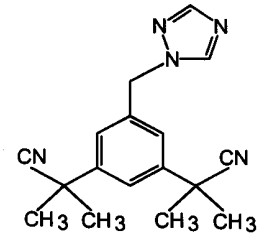
APPROVAL REPORT

The outcome of the evaluation by the Pharmaceutical and Medical Devices Evaluation Center pertaining to the drug noted in the Schedule for which an application for approval has been made is reported herewith.

Schedule

Proprietary name	Arimidex Tablets
Generic name	Anastrozole
Applicant	AstraZeneca
Date of application	19 November 1999 (import approval application)
Dosage form, content	Film coated tablets containing 1 mg as anastrozole per tablet
Category of application	1-(1) Drug containing new active ingredient

Chemical structure:



($C_{17}H_{19}N_5$; m.w. 293.37)

Chemical formula

2-[3-(1-cyano-1-methyethyl)-5-(1H-1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropanenitrile

Division responsible for Evaluation: Evaluation Division 1

OUTCOME OF EVALUATION

Prepared 24 October 2000

Proprietary name	Arimidex Tablets
Generic name	Anastrozole
Applicant	AstraZeneca
Date of application	19 November 1999 (import approval application)

Result of Evaluation

From the findings of the Japanese and foreign clinical studies submitted on this occasion as regards efficacy, the pharmacokinetics and pharmacodynamic effect of this agent in Japanese and Western subjects (inhibition of blood estradiol (E_2) concentration) would appear to be of a similar degree. As a dose-finding study has furthermore been conducted in Japan, it is considered that a complete clinical data package on anastrozole has been assembled and it is recognized as effective as an endocrinotherapeutic agent in post-menopausal breast cancer. In view of the findings of clinical studies conducted in Japan and overseas, posology involving a usual clinical dose of 1 mg once a day is judged to be valid.

As it is suggested that the adverse event profile found with this drug does not differ from that found overseas, it may be judged that its safety in Japan can be assured.

As a result of review by the Pharmaceuticals and Medical Devices Evaluation Center, it was judged that Arimidex may be approved for the following uses and posology.

Uses
Post-menopausal breast cancer
Posology
The usual adult dose is 1 mg as anastrozole taken once daily by mouth.

EVALUATION REPORT (1)

Prepared 21 August 2000

1. Product

Proprietary name	Arimidex Tablets
Generic name	Anastrozole
Applicant	AstraZeneca
Date of application	19 November 1999 (import approval application)
Uses applied for	Post-menopausal breast cancer
Posology applied for	The usual adult dose is 1 mg as Anastrozole given once daily by mouth.

2. Outline of materials submitted and outline of evaluation

I) Data on origin or course of discovery and usage in foreign countries, etc.

Anastrozole is a triazole antitumour agent with aromatase inhibitory activity discovered and developed by AstraZeneca of the UK (formerly ICI of the UK). Aromatase inhibitors suppress aromatases which govern the conversion to estrogen of adrenal-derived androgens in peripheral adipose tissue acting as the route of estrogen synthesis in post-menopausal women, and they consequently lower plasma estrogen. There are some breast cancers with intracellular estrogen receptors (ER) which replicate in an estrogen-dependent manner. As anastrozole is expected to be effective in the treatment of breast cancer exhibiting estrogen-dependent replication by lowering plasma estrogen in post-menopausal breast cancer patients, it has been developed as a therapeutic drug for endocrinotherapy.

As of July 2000, anastrozole has been approved as secondary therapy for post-menopausal breast cancer (for cases who have failed to respond to standard therapies) in 79 countries overseas such as the UK and USA and it is also approved as primary treatment in 18 of these including Europe.

The development of anastrozole in Japan has been conducted with reference to the findings of foreign clinical studies which had already been taken to early Phase II at the point when Japanese development was begun. In order subsequently to be able to extrapolate the European and American data to Japanese subjects, a bridging study on the clinical pharmacology in post-menopausal healthy females and a study as a

bridging study similar to a double blind trial with tamoxifen (TAM) conducted in Europe on potency were conducted in Japan. An evaluation jointly with the foreign studies was undertaken and an application for approval to import anastrozole made.

II) Data on physicochemical properties, specifications, test methods, etc.

The structure of anastrozole has been determined from element analysis, its infrared absorption spectrum, nuclear magnetic resonance spectrum and mass spectrum.

Specifications for the drug substance have been set in respect of content, description (XXX and solubility), identification tests (XXX), purity tests and assay method.

Specifications for the medicinal product have been set in respect of content, description, identification tests and assay method.

As the column used in the chromatogram of anastrozole could not be identified, the Pharmaceuticals and Medical Devices Evaluation Center (hereinafter called the "Evaluation Center") asked the applicant for details of the column used. The applicant responded that it was a stainless steel tube of XXX mm i.d. and XXX cm long packed with XXX μm XXX for liquid chromatography and XXX for liquid chromatography (XXX Co.; product name: XXX). In respect of this response, the Evaluation Center asked the applicant to provide information such as the mix ratio between the XXX and XXX. The applicant approached the manufacturer of the column for information but was told that this was a patent-related industrial secret and that the information could not be divulged. They therefore submitted a response that they would comply by providing the manufacturer's and product name of the column instead of the mix ratio as follows:

> " a stainless steel tube of XXX mm i.d. and XXX cm long packed with XXX μm XXX for liquid chromatography and XXX for liquid chromatography (XXX Co, XXX or equivalent)."

The Evaluation Center accepted this response as reasonable.

As diethylether is used as the XXX, the Evaluation Center asked the applicant about the solubility of the drug substance in diethylether in the solubility item in the description. The applicant investigated solubility in diethylether and consequently responded that they would add 'slightly soluble in diethyl ether' for the solubility item in the drug substance description.
The Evaluation Center accepted this.

The Evaluation Center asked the applicant to indicate the items investigated and actual data for the XXX and assay method for the drug substance and XXX, assay method and intermediate XXX reproducibility for the medicinal product. The applicant provided the items investigated and actual data for each of these. As the Evaluation Center considered amongst these that the evaluation of intermediate reproducibility precision for the assay method and XXX was inadequate, it asked for an evaluation based on an experimental protocol (preferably as least 6 test days) which would permit the influence of random variables for factors such as test date, tester and apparatus to be evaluated. The applicant thus submitted evaluation results for a total of 24 days with 6 test days, 2 testers and 2 apparatus systems. Evaluations biased to test date as the variable factor were found as a result of this, and the Evaluation Center sought a reanalysis so that there would be no bias and also asked the reason why XXX had not been investigated, as this could be imagined to be a variable. In response, the applicant conducted experiments on a total of 8 days with two testers, two apparatus systems and XXX and resubmitted the results of the evaluations.

The Evaluation Center regarded the analysis in this response as satisfactory and accepted it.

Considering that, under conditions at which the dissolution test specification can elucidate differences between lots and changes in dissolution rate properly, those standards must be able to assure bioequivalence, the Evaluation Center asked the applicant to compare dissolution behaviour using products from different lots, with different particle diameters, with development stage product and products changed over time to explain the validity of XXX and validity of establishing XXX minutes as the specification value from the point of view of assuring bioequivalence. The applicant responded to this as follows.

Upon conducting tests using XXX at a paddle speed of XXX rpm in order to select the dissolution test solution for anastrozole, similar dissolution behaviour was exhibited at all XXX but beyond XXX minutes after the start of the test, varying the paddle speed had no great effect on dissolution behaviour. As a result of these investigations, XXX was selected as the dissolution test solution. Furthermore, upon producing and investigating tablets using a drug substance with different XXX in order to examine XXX and the effect of dissolution behaviour, dissolution behaviour was unaffected. When the specification values were reconsidered in the light of this, the text was changed from 'The product meets the specification when its XXX minute dissolution factor is not less than XXX %' to The product meets the specification when its XXX minute dissolution factor is not less than XXX%'.

The Evaluation Center considered this to be valid and accepted it.

In the structural determination, the Evaluation Center also had asked for the IR spectrum to be changed to a diagram free of signals due apparently to moisture contamination and in the ^{1}H-NMR spectrum, had it made clear in the data summary that the signals which appeared near 2.5 ppm and 3.4 ppm were derived from deuterated dimethylsulphoxide used as the vehicle and from the moisture content thereof.

III) Data on stability

Severe tests, accelerated tests and long-term storage tests were conducted on the drug substance taking XXX, moisture content, XXX and content as test items. Although very slight variations in the moisture content and content were noted as a result, no increase in related substances or degradants was found, nor were any changes over time observed in the other measured items.

The product was subjected to severe tests, accelerated tests and long-term storage tests taking XXX, moisture content, hardness, XXX and content as test items. Very slight variation in hardness was consequently noted but no changes over time were observed in the other measured items and it was clear that the product was stable.

The Evaluation Center therefore judged from the above data that there was no problem with the stability tests.

IV) Data on acute toxicity, subacute toxicity, chronic toxicity, teratogenicity and other forms of toxicity

A single dose toxicity study was conducted using mice, rats and dogs. The approximate lethal oral dose was judged to be 250 mg/kg or more in mice, 100-250 mg/kg in rats and 45 mg/kg or more in dogs, and by intravenous administration, 50 mg/kg or more in mice and by intraperitoneal administration 50-250 mg/kg in rats. The principal observations were sedation, decreased respiratory rate and hunched-back position etc.

The multiple dose toxicity studies were conducted by oral administration using rats and dogs. In the one- and 6-month studies in rats, variations in haematology and serum biochemistry items were found at 5 mg/kg and over, as were enlarged hepatocytes due to enzyme induction and, in females, changes attributed to the pharmacological action of the drug on the reproductive organs (enlargement of the ovary, increases Graafian and cystic follicles, increased corpora lutea, etc.). The non-toxic dose was judged to be 1 mg/kg in both studies. In the one, 6 and 12 month studies in dogs, hepatic hypertrophy accompanied by centrilobular hepatocytic hypertrophy attributed to enzyme induction, hepatocyte necrosis in the 8 mg/kg group in the 6-month study and decreased R wave amplitude in the ECG in the 12 mg/kg group in the one month study and 8 mg/kg group in the 12 month study were noted. Changes in the reproductive organs associated with the pharmacological activity and variations in haematological and serum biochemical test items were also observed. The non-toxic dose level was 3 mg/kg in the one, 6 and 12 month studies.

Reproductive and developmental toxicity studies were conducted by oral administration to rats and rabbits. In the fertility study in female rats, decreased pregnancy rates, decreased numbers of implantations and live fetuses and increased numbers of pre-implantation deaths were observed and the possibility was considered that implantation had been impeded by the decreased level of estrogen prior to implantation due to the pharmacological activity of the drug. Delayed fetal development was observed in the teratogenicity study in rats but no teratogenic action was identified. In the teratogenicity study in rabbits, decreased pregnancy rates were seen and the possibility that the drug had acted directly on fertilized eggs and obstructed implantation was considered. In the rat perinatal and lactation study,

decreased birth rats, increased numbers of dams with all-stillborn litters and decreased three month-survival rates were noted. The non-toxic dose levels in the reproductive and developmental studies were 0.02 mg/kg in terms of general toxicity to dams, 0.002 mg/kg in terms of reproductive performance, 0.002 mg/kg to foetuses and 0.02 mg/kg to the offspring.

Genotoxicity was studied through reverse mutation tests using bacteria, genetic mutation and chromosomal aberration tests using cultured mammalian cells and micronucleation tests using rats, all of which gave negative results.

Carcinogenicity studies were conducted using mice and rats. In mice, increases in benign ovarian tumours were found in all groups treated with the test substance. It was discussed that these increased ovarian tumours seemed to have been caused by increased secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary brought about by the lower levels of estrogen due to the pharmacological activity of the drug. In rats, increases in thyroid tumours were noted in males and liver tumours in females. As causes for this, it was considered that thyroid hormone metabolism may have been promoted by the liver drug metabolizing enzyme-inducing activity of the drug and that the secretion of thyroid stimulating hormone (TSH) from the pituitary had consequently been enhanced, irritating the thyroid follicular epithelium. As regards the increased liver tumours, the possibility was discussed that the estrogen-androgen balance had been upset by the anti-aromatase activity of the drug, or that induced drug metabolizing enzymes in the liver had caused changes in hepatocyte replication.

Local irritation studies were conducted using skin and ocular mucosa from rabbits but no irritation was noted with either of these.

Antigenicity was studied through active systemic anaphylaxis (ASA), homologous passive cutaneous (PCA) tests, contact sensitization tests and heterologous PCA using mice and rats, but all gave negative results.

No experiments were conducted on the toxicity of related substances but in view of the findings of the multiple dose studies and the like, it was considered that there would be no problems of toxicity.

The Evaluation Center sought the view of the applicant regarding the definitions for toxic and non-toxic dose levels in the toxicity studies. The applicant

responded that in defining non-toxic dose levels, they had used the somewhat vague term of ‘serious toxic change', and given the specifics for each study. They proposed that the definition of non-toxic dose should be dropped from the Summary (Gaiyo). Upon reassessing the toxicity study findings, although they considered there would be little possibility of extreme adverse effects on survival and the function of other organs, the values for some of the test items deviated considerably from the background levels and as the possibility of biological harm could not be ruled out, they felt that these should be regarded as toxic findings and that changes should be made to the non-toxic doses identified.

The Evaluation Center accepted this.

The non-toxic dose in the 12-month dog study has now been altered from 6-8 mg/kg to 3 mg/kg due to the increases in platelets, ALP and ALT, and in the rat teratogenicity study from 0.1 mg/kg to 0.02 mg/kg due to the deaths of some dams.

Regarding the long term safety of anastrozole, some discussion of its effects on hepatocytes (carcinogenicity etc) in comparison with tamoxifen (TAM) had been asked for. The applicant replied that effects on hepatocytes had been investigated in a two-year carcinogenicity study on anastrozole and that increased hepatocytic carcinomas and hepatocyte adenomas had been noted only in the final stages of treatment in females only in the 25 mg/kg (highest dose) group. With TAM, on the other hand, increased tumours had been noted from early in the treatment period at low dose levels (Cancer Res. 53: 3919, 1993). The cause of this is known to be that TAM and its metabolites form adducts with rat hepatocyte DNA and a mechanism involving genotoxicity may be imagined (IARC Monographs 66:253, 1996). In view of these facts, whereas TAM induces liver tumours thought to be caused by genotoxicity from the early phase of treatment, anastrozole induces liver tumours thought to be due to some phenobarbital-like enzyme inducing activity and the mechanism of tumorigenesis seems clearly different.

The Evaluation Center accepted this.

From the findings of an extension study, the applicant had inferred a mechanism involving phenobarbital (PB)-like action for the thyroid tumours found in

the rat carcinogenicity study. As PB increases uridine-5'-diphosphate glucuronate transferase (UDPGT) in the liver and consequently promotes thyroxine (T4) metabolism, it is believed to act as an anti-thyroid agent. However, the levels of T4 and free T4 in the blood had both shown significant rises in the extension study and the Evaluation Center asked the applicant's view on this. The applicant replied that the cause of this seemed to be that with multiple doses of PB, TSH and T4 do not change from the level immediately after the start of administration to a constant level but vary greatly during this time, settling to a range not greatly different from the normal state after 4-8 weeks. In this study on the other hand, measurements had been taken only before and at the end of the 30-day treatment period and there was no detailed information on the course of TSH and T4 levels in the blood, but it could be inferred that T4 and free T4 had not yet achieved a steady state. The measurements at 30 days indicated a rise in TSH and because the thyroid would have been stimulated by this rise and hormone secretion would have exceeded T4 clearance, the plasma level of T4 and free T4 would also have risen.

This response was accepted.

The applicant had claimed that the cause of the chronic, progressive glomerulonephritis (CPGN) noted in the 6 month multiple dose toxicity study in rats had been high protein intake due to excessive food consumption, but because it is not infrequently caused by obstruction of the urinary pathway, the Evaluation Center asked for comments on this point. As CPGN is also known to occur more frequently in males than in females, the Review Center sought an explanation as to whether the present findings could have resulted from masculinization of the female rats due to administration of the test substance. The applicant had re-checked the histopathological findings but because no changes had been noted in the urinary tubules and no variations in urine volume had been noted, had inferred that there was little possibility that the passage of urine through the urinary pathway had been impaired. Increased food consumption and increased plasma protein were considered as causes of this change but as there was no clear correlation with food consumption, there was little possibility of its involvement and the possibility that it had been caused by increased total protein in the blood caused by the variation in estrogen could be

imagined. Histological changes in the adrenal and decreased adrenal and pituitary weight were noted as changes suggestive of masculinization of the females and the possibility could not be ruled out that the variations in estrogen brought about by administration of the drug had caused masculinization of the female rats and increased total protein in the blood leading to the increased incidence of CPGN which is more common in males.

The Evaluation Center accepted this explanation.

V) Data on Pharmacology

Investigations through pharmacological studies to support its potency indicated that anastrozole inhibited testosterone-induced DNA synthesis from 10^{-8}M. It also provided marked control of the proliferation of breast cancer induced in rats by 7,12-dimethylbenz[a]anthracene (DMBA) at 10 mg/kg/day (given orally once daily for six weeks), and tumour growth in ovariectomized nude mice implanted with MCF-7_{CA} cells transfected with the aromatase gene was also significantly inhibited at 5 μg/mouse/day (given subcutaneously once daily for six weeks).

Investigation of the mechanism of action indicated that anastrozole inhibited human placenta aromatase in a concentration-dependent manner with IC_{50} of 14.6 nM. The activity of anastrozole compared in terms of the IC_{50} was approximately 200 times more potent than aminoglutethimide, approximately twice as potent as formestan and approximately one third as potent as fadrozole. It was further held to have significantly inhibited aromatase at 10^{-8}M in the human breast cancer cell line MCF-7. Single oral doses of anastrozole from 0.1 mg/kg was completely suppressed ovulation in mature rats and its potency was approximately 200 times that of aminoglutethimide and about the same as fadrozole. The oral administration of 0.05 mg/kg/day and over of anastrozole also significantly inhibited the uterine hypertrophy effect of androstendione in juvenile female rats. Oral doses of 0.01 mg/kg and over of anastrozole (twice daily) furthermore significantly lowered plasma estradiol (E2) in mature male monkeys in a dose-dependent manner and its potency was judged to be virtually equivalent to that of fadrozole.

Upon investigating the selectivity of its action, no action to increase adrenal weight was demonstrated with 7 or 28 days administration to rats or 28 days to dogs.

Aminoglutethimide which is known to obstruct cholesterol side chain cleavage (CSCC) significantly increased adrenal weight whereas fadrozole was held not to have shown any weight-increasing effect on the adrenals. The *in vitro* IC_{50} of anastrozole for inhibition of 11β-hydroxylation was 4.1 μM (guinea pig), 129.5 μM (dog) and 11.8μM (cow), all of which were judged to be weaker actions than for fadrozole. Even when administered at 30 times the dose level providing significant lowering of E2, anastrozole had no significant effect on the plasma concentration of 11-deoxycorticosterone (11-DOC) in male monkeys and as it also had no significant effect on the plasma level of aldosterone in male rats, it was considered not to obstruct 18-hydroxylation. Because it furthermore showed no significant activity in respect of Na^+ and K^+ excretion in saline-loaded rats, it was considered not to obstruct 11β- and 18-hydroxylation in rats. As anastrozole had no significant effect on plasma testosterone in male rats nor on LH levels and reproductive organ weight and also failed to raise plasma testosterone in monkeys and dogs, it was believed not to inhibit androgen biosynthesis. In *in vitro* tests, anastrozole was held not to act on cholesterol or lanosterol biosynthesis with rat and dog hepatic microsome fractions, and not to affect plasma cholesterol in rats in *in vivo* tests. Significant lowering of plasma cholesterol had been noted on day 12 of treatment in the one-month oral toxicity study on anastrozole in dogs, but partial reversal had taken place by day 28.

M2, the major plasma metabolite of anastrozole in rats, dogs and man was stated not to impair E2 and progesterone secretion in rat granular membrane cells in an *in vitro* study, female rat ovulation was not inhibited even with oral administration up to 100 mg/kg, nor did it even affect adrenal and hepatic weight in male rats. With the other metabolites, the urinary and bile metabolites M4 (rat and dog) and M3 (rat, dog and man) fully inhibited rat ovulation at respectively 1 mg/kg and 10 mg/kg but as these metabolites were not detected in the plasma of rats, dogs and man, they were believed to have been hardly involved at all in the aromatase inhibiting activity of anastrozole in the *in vivo* studies.

In the general pharmacology studies, *in vitro* tests had indicated activation of β2 receptors (isolated guinea pig trachea strips and rat isolated gravid uterus) and 5-HT_1 receptors (rat isolated gastric fundus strips) at anastrozole concentrations of 10^{-5} or 10^{-4} anastrozole. A significant increase in spontaneous motor activity was seen with

oral administration of 10 mg/kg anastrozole to mice, as were lowered blood pressure, shortened PR and QT intervals with oral administration of 10 mg/kg to dogs but no such effects were noted at 1 mg/kg. Oral administration of 10 mg/kg/day led to a slight inhibition of delayed hypersensitivity reactions in mice but this effect was not seen at 1 mg/kg/day. Furthermore, the dose in the *in vivo* tests is judged to correspond to about 50 times the clinical dose level and the concentration of 10^{-5}M used in the *in vitro* tests to about 63 times the maximum plasma concentration (Cmax) found in the steady state with the administration of multiple oral doses to man. Nothing posing any particular problem was noted in terms of gross symptoms and behaviour, actions on the somatic nervous system, respiratory system, gastrointestinal system, water and electrolyte metabolism, blood coagulation and fibrinolysis system and reproductive system (except the aromatase-inhibiting action) and anti-inflammatory actions.

The Evaluation Center asked the applicant whether there were any findings comparing the antitumour effect of anastrozole and analogues. The applicant responded that they had not undertaken any studies comparing the antitumour effect of anastrozole with analogues, the reason for this being that there is no good model reflecting the activity of aromatase inhibitors in human post-menopausal breast cancer, and that as the half life of anastrozole in rat and mouse plasma ($t_{1/2}$: respectively 2.3-4.9 and not more than 1 hour) is much shorter than in man (55.9 hours), it may be anticipated that the potency ratio of the antitumour effect of multiple doses of anastrozole and analogues would differ from man. They had therefore compared it with the like-acting drug fadrozole not in terms of antitumour effect, but in terms of anti-aromatase activity and inhibition of the biosynthesis of steroid hormones other than aromatases. The Evaluation Center asked the applicant to compare the antitumour effect of anastrozole with TAM or other anti-estrogen agents and to explain the therapeutic ranking of anastrozole in terms of its pharmacological activity. A reply was given to the effect that in the model of DMBA-induced rat breast cancer, the antitumour effect of aromatase inhibitors is affected by feedback from the hypothalamus-pituitary-ovarian system; that in the ordinary model involving the transplantation of breast cancer cells into nude mice, the administration of estrogen is needed for tumour growth and it may be imagined that the effect of aromatase inhibitors would be scarcely evaluable; and that whilst there is a model involving the

transplantation of human breast cancer cells MCF-7_{CA} into ovariectomized nude mice, unlike in man, aromatase localizes in the brain and transplanted MCF-7_{CA} cells, and the mice are also given the aromatase substrate androstendione. For such reasons as these, they held that the antitumour effect in these models would not accurately reflect the response of breast cancer in post-menopausal women, and it could not be said that the potency ratio against post-menopausal breast cancer in the clinical setting would be reflected accurately by comparing the antitumour effect of an aromatase inhibitor and anti-estrogen agent in an animal model of breast cancer. The therapeutic ranking of anastrozole should therefore be based on the results of clinical studies.

The Evaluation Center accepted these arguments.

Because there seemed to be no need to stress the selectivity of anastrozole activity unless clinical dose levels of analogues with aromatase inhibiting activity also affected the routes of steroid hormone biosynthesis, the Evaluation Center requested the applicant to provide a comparative discussion with analogues about selectivity of action taking account of clinical dose levels. The response stated that the findings of a study on action selectivity between anastrozole and fadrozole had indicated that its aromatase inhibitory activity in the *in vivo* studies (inhibition of ovulation in mature rats and action on plasma E2 levels in male monkeys) was of the same order as fadrozole. However taking account of the fact that fadrozole as well as inhibiting aromatase, affects 11β-hydroxylation (monkey plasma deoxycorticosterone concentration) and 18-hydroxylation (rat plasma aldosterone concentration etc.) and in particular that its inhibition of 11β-hydroxylation is seen at 2.5 times the dose at which it inhibits aromatase, and that fadrozole has been reported to lower plasma aldosterone in the clinical situation (Cancer and Chemotherapy 21:465, 1994, Cancer and Chemotherapy 21:485, 1994) whilst no such activity has been observed with anastrozole, the fact that there has been a proper differential in animals between the dose providing aromatase inhibition and the dose inhibiting the biosynthesis of other steroid hormones is important from the point of view of safety.

The Evaluation Center accepted this response. Furthermore, as regards the mechanism of action and selectivity of the activity of anastrozole, the Evaluation Center asked the applicant not only to clarify the dose ratios of anastrozole and its

analogues for the aromatase-inhibiting dose and the dose levels inhibiting the various enzymes but also to provide table(s) and diagram(s) relating to the active mechanism of the drug including various hormone therapeutic agents and advised that the data should be arranged so as to make the active points of the drug clear.

The Evaluation Center also asked the applicant about the active mechanism of anastrozole as regards its inhibition of plasma E2.

It is known that estrogen is synthesized mainly in peripheral tissue such as adipose tissue in post-menopausal females (J.Clin.Oncol, 12: 2460, 1994). Aromatase is present mainly in peripheral tissue such as adipose tissue (Breast Cancer Res. Treat. 50:63, 1998). Aromatase is an enzyme involved in the final stage of estrogen synthesis and is selectively inhibited by anastrozole. Aromatase activity ($x10^{14}$ mol/mg protein/h) in the mammary tissue of eight human breast cancer cases was 1.1 ± 0.15 times in normal tissue and 2.51 ± 0.24 at the tumour site (Clinical Breast Cancer 11: 415, 1996). An investigation of tissue estrogen levels ($x\ 10^{-9}$ mol/g tissue) in 61 normal post-menopausal breasts and tissue from 65 cancerous breasts indicated (estrone (E1) 7.1, E2 9.3) in healthy breast tissue and (E1 9.0, E2 13.4) in cancerous breast tissue (Int J. Cancer 40:305, 1987). These reports demonstrated a marked trend for aromatase activity and estrone concentrations to be higher in neoplastic tissue than in normal breast tissue. However, aromatase activity in neoplastic tissue is reported to be much lower than the activity of other enzymes involved in estrogen production (estronsulphatase, 17β-hydroxysteroid dehydrogenase (17β-HSD) (Clinical Breast Cancer 11: 415, 1996). There is currently no set view on how aromatase in neoplastic tissue is involved in the maintenance of elevated estrogen in neoplastic tissue.

In a study on the estrogen-lowering activity of anastrozole in neoplastic tissue (Proc. Am. Soc. Clin. Oncol. 18:82a, 1999), the recommended clinical dose of 1 mg/day of anastrozole was given as pre-surgical endocrinal therapy to post-menopausal breast cancer patients for 15 weeks (median period) and the levels of estrogen in the neoplastic tissue was measured pre- and post-administration. The E2, E1 and estronesulphate (E1S) levels in neoplastic tissue from the 12 assessable cases had been inhibited respectively 11.1% (4.6-27.2%), 16.7% (7.5-36.9%) and 26.6% (14.2-49.7%) of the baseline value (mean(95% confidence interval)). This could be considered to have been due to the anti-aromatase action of anastrozole and decreases in the base

amounts of estronesulphatase and 17β-HSD due to the inhibition of aromatase (respectively E1S and E1) (Protocol No. 1033IL/0022). The baseline levels of E2 and E1 in breast cancer tissue (mean values) had been respectively 2.2 x 10^{-10}M and 1.7 x 10^{-10}M (calculated taking 1 g of tissue to be 1 mL) and after treatment, the levels were respectively 2.4 x 10^{-11}M and 2.8 x 10^{-11}M. It has been reported that the promotion of DNA synthesis by E2 and E1 in *in vitro* studies with the human breast cancer cell line MCF-7 is dose-dependent at respectively 10^{-12}~10^{-10}M and 10^{-12}~10^{-9}M and that a plateau is reached at levels above these (J. Steroid Biochem. Mol. Biol 42: 267, 1992). It was suggested that the estrogen-inhibiting effect in breast cancer tissue resulting from the administration of anastrozole would be in the range at which activity against the replication of breast cancer cells could be induced.

Anastrozole decreases plasma E2 and E1 levels but it is not clear to what degree the inhibition of aromatase in peripheral tissue and plasma estrogen concentrations is involved in lowering the level of estrogen in breast cancer tissue. Plasma E2 (x 10^{-12}M) in six post-menopausal breast cancer cases before and after treatment with 1 mg/day anastrozole for one week was respectively 42.0 ± 17.1 and 4.0 ± 2.0. Bearing in mind the investigations of estrogen levels in neoplastic tissue from breast cancers mentioned earlier, anastrozole may be considered to reduce estrogen both in plasma and in breast cancer tissue. It would seem possible from these results that the anti-tumour effect of anastrozole could be estimated by determining the plasma E2 concentrations and confirming a reducing action.

In view of the facts that [1] the principal active mechanism of anastrozole may be inferred to be that it inhibits aromatase activity in breast cancer tissue and that as a result of the decreased estrogen level, acts indirectly to inhibit hormone-dependent proliferation in the tumour, [2] decreased plasma E2 levels may be expected to some degree to reflect decreases in E2 in neoplastic tissue and [3] the density of estrogen receptors in tumour cells differs from case to case and the response to endocrinal treatment amongst estrogen receptor-positive breast cancer patients may also be expected to differ depending on the patient (Br. J. Cancer 60:223, 1989), the Evaluation Center judged that whilst decreases in blood E2 reflect the pharmacological activity of anastrozole, an anti-tumour response in breast cancer cannot be predicted with certainty (Ann. Oncol. 11: 1017, 2000).

VI) Data on absorption, distribution, metabolism and excretion

Anastrozole was absorbed rapidly in rats and dogs, with percentage absorption of 83% or more upon oral administration of 1 mg/kg. Its bioavailability was also 82% or more but that value rose with increases in the dose and this was concluded to suggest saturation of elimination. However, with multiple oral doses of anastrozole, it was considered that the saturation of elimination tended to be cancelled out by the enzyme-inducing action.

Gender difference was noted in the elimination of anastrozole in rats, with systemic clearance in males upon intravenous administration being four times that in females. The elimination half life ($t_{1/2}$) of the drug was also 2.1 hours in males but 5.6 hours in females. In dogs on the other hand, $t_{1/2}$ was about the same at 10 hours in both males and females.

When rats were given a single oral dose of ^{14}C-anastrozole, radioactivity was distributed widely to the tissues, with the peak levels being reached in the majority of tissues one hour after the dose. High levels of radioactivity were noted in the liver, adrenal and preputial glands in both males and females. Elimination from the various tissues was relatively rapid, with radioactivity 168 hours after the dose falling to less than 3% of its peak level. Furthermore, with multiple once-daily oral doses for ten days, plasma radioactivity rose about three-fold and radioactivity accumulated in the individual tissues to much the same degree or less than in the plasma. ^{14}C-anastrozole was observed to cross the placenta when administered orally to pregnant rats and pregnant rabbits, with foetal radioactivity being 38 - 46 % of the plasma level in the dam.

Plasma protein binding of the drug in the rat, dog, mouse, rabbit and monkey was low at 16.5 - 42.1 % and remained virtually constant irrespective of the concentration of the drug. When rats and man were dosed with ^{14}C-anastrozole, the distribution of radioactivity to the haemocytes was respectively 13.7 - 30.8 % and 28.6-32.7 %.

When its effects on the drug metabolizing enzyme system were investigated in rats and dogs, enzyme induction similar to phenobarbital was noted. Moreover, inhibitory activity against pentobarbital metabolism in the rat and antipyrine metabolism in the dog were suggested. A gender difference was noted in the excretion

route for XXX, the major metabolite in rats. In males this was excreted mainly in the bile and in females, about equally in the urine and the bile.

In dogs, on the other hand, the radioactivity was excreted mainly in the urine and no clear gender difference was apparent in the percentages of radioactivity excreted in the urine and bile.

Following a single oral dose of 1 mg of anastrozole to healthy post-menopausal women, absorption was relatively rapid, with the time taken to reach the maximum plasma concentration (Tmax) being 1.3 hours. It was eliminated biphasically with t1/2 of 56.3 hours. When multiple doses were given on a once-daily basis, a steady state had been reached by the tenth dose and accumulation was 3.7 *(%)*. Linearity over the range 1-20 mg was suggested from the course of the plasma levels of the drug in foreign subjects.

When post-menopausal cancer patients were given doses of 1, 5 and 10 mg anastrozole once daily for 8 weeks, the plasma concentration of the drug increased virtually in proportion to dose. It has also been inferred that the plasma level of anastrozole achieves an almost steady state upon giving multiple doses for one week. Accumulativity is predicted to be around 3-4 % and t1/2 about 50 hours. When, moreover, the relationship between the trough plasma level of anastrozole in the steady state and age was investigated in foreign breast cancer patients, there was judged to be no clear causal relationship between the two.

The plasma concentration of anastrozole in Japanese and foreign postmenopausal women followed a similar course and there was held to be no statistically significant difference in a comparison of the trough concentrations with multiple once-daily doses in the bridging study on clinical pharmacology.

When the metabolism and excretion of anastrozole were investigated in postmenopausal females (foreign) given a single oral dose of 10 mg ^{14}C-anastrozole, the excretion of radioactivity in the urine and faeces up to 14 days after the dose was respectively 71.2-74.6 % and 8.7-13.6 %, and from the ratio of urinary radioactivity excretion relative to the total recovery of radioactivity, the absorption of the drug seemed to be 84% or more.

Upon investigating the effects of hepatic and renal impairment at the anastrozole dose level of 10 mg, the plasma level of the drug was unaffected by renal impairment but Cmax increased in patients with hepatic impairment. However, as no effects on $AUC_{0\text{-}inf}$ were seen in hepatically impaired patients and good tolerability was demonstrated at even ten times the recommended clinical dose, there was judged to be no need for dose adjustment in such patients.

When effects on the activity of cytochrome P450 in human liver microsomes were investigated, whilst the activity of CYP1A2, CYP2C8/9 and CYP3A4 was inhibited, it was predicted that the capacity to inhibit P450 seen in the *in vitro* tests would not pose any clinical problem in view of the plasma levels in man. No drug interactions in pharmacodynamic terms were noted upon investigating drug interactions on antipyrine, warfarin and TAM with the co-administration of anastrozole, confirming that the capacity to inhibit P450 seen in the *in vitro* tests would not pose any clinical problem. No effects on the metabolism of anastrozole were noted with the co-administration of cimetidine (a non-specific P450 inhibitor).

As it is held that anastrozole shows no enzyme inducing activity following administration, but that enzyme induction for autometabolism was seen in rats and dogs upon giving multiple doses, the Evaluation Center asked the applicant to discuss the disparity of enzyme inducing activity seen between man and rats and dogs, the possibility of enzyme induction for autometabolism with long term use in man and the need for such information to be reflected in the package insert. The applicant replied that anastrozole had shown dose-dependent enzyme induction in rats and dogs but as the dose administered to man was not more than 10 mg and assuming human body weight of 50 kg and over, the dose at which enzyme induction had been seen in rats and dogs was more than five times the dose administered to man, so that the disparity in dose levels used in the studies may well have contributed to the discrepancy in enzyme induction between man and rats and dogs. On the potential for enzyme induction with long-term use in man, Phase III studies conducted overseas in which cancer patients had been given multiple doses at one dose per day and their plasma anastrozole had been measured from 4 to 60 weeks treatment had indicated that even at ten times the recommended clinical dose (10 mg) for long periods, no clear decrease in

plasma anastrozole was seen and there seemed to be hardly any possibility of enzyme induction for autometabolism if used at 1 mg in the clinical setting. However, in order to provide information about the metabolism of the drug, they would include an account of the findings for enzyme induction seen in rats and dogs and the results of the clinical studies in the section on pharmacokinetics in the package insert.

The Evaluation Center accepted this.

On the issue of drug interactions, anastrozole had been seen to have CYP1A2, CYP2C8/9 and CYP3A4 inhibitory activity *in vitro*, and the Evaluation Center therefore asked the applicant about the need for this information to be reflected in the package insert. The applicant made the following points about the possibility of drug interactions originating in enzyme inhibition, [1] the Ki value was 8-10 μM i2.3-2.9 μg/mL, about 50 times Cmax in the steady state in man (0.05 μg/mL approx.); [2] when clinical studies on drug interactions were conducted to investigate effects on the pharmacokinetics of antipyrine (CYP1A2, CYP2C9 and CYP3A4 involved in metabolism), warfarin (CYP1A2, CYP2C19 and CYP3A involved in the metabolism of R-warfarin, mainly CYP2C9 in that of S-warfarin) and TAM (mainly metabolized by CYP3A4), it was confirmed that their pharmacokinetics are affected by anastrozole; [3] clinical studies have confirmed that the pharmacokinetics of anastrozole are unaffected by cimetidine used as a non-specific P450 inhibitor; [4] there are no reports of clinically meaningful interactions from clinical studies conducted on anastrozole overseas; and [5] four instances of drug interaction have been noted in foreign postmarketing ADR reports but the possibility of interaction between anastrozole and the other drug was ruled out in each case. Since its overseas sales launch, there have to date also been in excess of 250,000 patient-years experience of its use. In view of all the above, it is inferred that the capacity to inhibit P450 seen in the *in vitro* studies poses no clinical problem and at the current time, they have judged there to be no need to discuss drug interactions in the Precautions and Warnings, but will provide the findings of the *in vitro* tests and clinical studies on interactions as reference data in the section on pharmacokinetics in the package insert.

The Evaluation Center accepted this reply.

On the question of comparing pharmacokinetics in Japanese and other ethnic groups, the Evaluation Center asked the applicant about the potential for extrapolation referring to the questions and answers about guidance on ethnic factors to be considered when accepting foreign clinical data (*Iyakushin* 672, 11 August 1998). The applicant replied that upon investigating the properties of compounds considered unlikely to be affected by racial factors as described in the 'Susceptibility of medicinal products to ethic factors' in Appendix D of *Iyakushin* Notice 672, they had inferred the possibility that anastrozole is unlikely to be affected by racial factors in view of its characteristics of linearity, pharmacodynamic curves, tolerability (therapeutic area), metabolism, bioavailability, protein binding, interactions and potential for misuse, and in order to verify this, had conducted a bridging study on clinical pharmacology as well as comparing the existing data for Japanese and foreign subjects. From the existing data for post-menopausal females, a comparison of the course of plasma anastrozole concentrations following a single oral dose of 1 mg of the drug obtained in Japanese and foreign studies indicated that they followed a similar course and that the pharmacokinetic parameters (Tmax, Cmax, $AUC_{0\text{-inf}}$ and $t_{1/2}$) were of the same degree. Upon also comparing oral clearance (CL/f) for all the dose group (dose range 0.5-20 mg) in order to check that the results of the comparing the 1 mg groups could be extrapolated to other dose levels, the CL/f of 16.8-20.7 mL/min found in Japanese subjects was similar to CL/f in foreign subjects (18.1-19.4 mL/min). It was therefore inferred that there was no great difference in the pharmacokinetics of anastrozole in Japanese and foreign subjects and these comparisons would seem to support the strong possibility that anastrozole is little susceptible to ethnic factors. Furthermore, comparing existing data for breast cancer patients (Protocol No. US0003) (Protocol No. IL0004: published in Eur J Cancer 32A:404, 1996), when Japanese or foreign breast cancer patients were given multiple, once-daily oral doses of anastrozole and trough plasma anastrozole in the steady state (Cmin) was measured, this was found to be almost proportional to the dose level, but Cmin tended to be slightly higher than in foreigners, the level per 1 mg of dose being 41.2-42.4 ng/mL in Japanese and 36.0-39.2 ng/mL in foreign patients. Although the possibility that body weight differences were involved in this trend could be inferred, because the pharmacodynamic curves for anastrozole were not steep and anastrozole was well tolerated even at ten times the

recommended clinical dose, the fact that Cmin in Japanese patients was slightly higher than in foreigners would not seem to represent any problem for the accepting of foreign clinical data.

The Evaluation Center accepted these responses.

The Evaluation Center furthermore asked the applicant to clarify the patient background characteristics in the hepatic impairment group in respect of the investigation on the effects of hepatic impairment on plasma anastrozole levels following administration of the drug. In reply, it was stated that the selection criteria for this study (Study No. IL0014) had been "subjects with alcohol-related chronic hepatic impairment evidenced by clinical or laboratory test findings and confirmed by liver biopsy" and although age, weight and baseline laboratory values and doctors' findings on screening had been given, no diagnosis listing had been provided for all the cases. However assuming that these hepatically impaired cases had no hepatic-related encephalopathy, the severity of hepatic change by Child-Pugh grading was grade A for all the patients and they had classified as having hepatic change with a good prognosis. In view of this grading and the liver enzyme values, severity of mild to moderate had been present in the patients investigated for the effects of hepatic impairment.

The Evaluation Center accepted this. The Evaluation Center asked the applicant about the need for the reports that anastrozole is mainly metabolized in the liver to be reflected in the package insert as they judged this to be necessary in terms of the pharmacokinetics, and accepted the response that based on UK findings, about 75% of the drug seemed to be metabolised and eliminated in the liver and that they would this report in the section on 'Pharmacokinetics' in the package insert.

VII) Data on Clinical Trial Results

A) Summary of data submitted

The following trials have been conducted in Japan.

1) Phase I study (Protocol No. A-15-11)

A study investigating safety, pharmacokinetics and antitumour response in cases of human post-menopausal previously-treated progressive or recurrent breast cancer (primary, ER of metastases positive or unknown) was conducted from August 1993 administering 1 mg/day (6 cases) 5 mg/day (6 cases) and 10 mg/day (8 cases) of anastrozole for 8 or more weeks. Adverse events for which causality by anastrozole could not be ruled out included one case of nausea, headache and dizziness in one case from the 1 mg group but these were mild and transient. Antitumour response of PR was found in two cases each from the 1 and 5 mg groups and one each of CR and PR in the 10 mg group. Plasma E2 had decreased in all groups after 24 hours and the decline was seen to persist even after one and 8 weeks.

2) Clinical pharmacology study (Protocol No. No.A-15-12)

A study investigating safety, pharmacokinetics and pharmacological activity was conducted from January 1995 administering 0.5 mg and 1 mg/day anastrozole (6 cases each) as a single dose and as multiple doses for 14 days (randomized, non-blind study). Adverse events for which causality by anastrozole could not be ruled out included one case of dull headache in the 1 mg single dose group, and with multiple doses, nausea and pain in the right leg in one case from the 0.5 mg group and vertigo, feeling of swollen extremities and sweating in one case from the 1 mg group, but these all disappeared without treatment whilst continuing with the drug. Plasma E2 (x 10^{-12} mol/L) measured at the Royal Marsden Hospital, before and 24 hours after 14 days administration was 35.2 ± 16.4 and 6.0 ± 3.5 in the 0.5 mg group and 25.3 ± 13.5 and 4.6 ± 2.3 in the 1mg group, suggesting that by day 14 of treatment the level of E2 had decreased more significantly with the dose level of 1 mg than 0.5 mg ($p=0.016$). The course of plasma cortisol, aldosterone, androstendione, testosterone, luteinizing hormone and follicle stimulating hormone was also investigated but no clear effects due to the administration of anastrozole were noted.

3) Early Phase II studies (Protocol No. A-15-21)

A dose-finding study (randomized, non-blind study) investigating antitumour response and safety was conducted from May 1995 administering 0.5mg/day (36 cases), and 1mg/day (34 cases) of anastrozole for 12 weeks to cases of progressive or recurrent human post-menopausal (age 51-80) breast cancer (primary, or ER of metastases positive or unknown). Antitumour response at the 12 week point after commencing administration was 2.8% in the 0.5mg group (1/36 cases, PR 1 case) and 20.6% in the 1mg group (7/34 cases, CR 2 cases, PR 5 cases). The main adverse events for which causality by anastrozole could not be ruled out were rises in LDH, lowered white blood cells, rises in GOT and GPT and vertigo, but nothing serious was noted.

4) Long term study (Protocol No. A-15-24)

Following on from the early Phase II study, a study on efficacy and safety on long-term administration for 24 weeks and over was conducted in the cases whose antitumour response had been assessed as NC or more at 12 weeks treatment with anastrozole. Continued treatment with anastrozole was given in 26 cases in the 0.5mg group and 28 cases in the 1mg group. The final success rates were 0.5mg group: 27.8% (10/36 cases, CR 1 case, PR 9 cases) and 1mg group: 41.2% (14/34 cases, CR 2 cases, PR 12 cases). Moreover, the median treatment period and deterioration-free period were respectively 0.5mg group: 32.6 weeks and 271 days, and 1mg group: 34.4 weeks, and 188.5 days. Newly encountered adverse events other than as observed in the early Phase II study and for which causality by anastrozole could not be ruled out comprised one case of cervical pain and one of vaginal discomfort in the 1 mg group.

From the findings of the early Phase II study and long-term study in post-menopausal breast cancer and the clinical pharmacology study in healthy post-menopausal females, it was judged that as the dose level of 1 mg/day of anastrozole had provided greater levels of antitumour response and greater inhibition of E2 levels in the blood than 0.5 mg, the recommended clinical dose in Japan should be 1 mg per day p.o.

5) Bridging study on clinical pharmacology (Protocol No. 1033IL/0035; Publication: Cancer Chemother Pharmacol 46:35, 2000)

From the findings of the four studies from Phase I to the long term study conducted on anastrozole in Japan and the results of comparative investigations with the foreign clinical studies (Protocol No. 1033US/0003: Publication: Steroid Biochem Mol Biol 59:439, 1996; Protocol No. 1033IL/0022, Protocol No. IL0019), the efficacy and safety of anastrozole appeared very similar in Japanese and Western subjects and it was judged that it would be possible to extrapolate the foreign clinical data if an appropriate bridging study were undertaken.

A study to compare the pharmacokinetics and pharmacological activity of 1 mg/day of anastrozole for 16 days in healthy post-menopausal females in Japan, Europe and America (non-controlled, non-blind, Japanese-Western intergroup comparison) was conducted from XXX (mth) XXX (year). 24 Japanese women (mean age 60.9 years (50-73)) and 24 Western women (61.5 years (52-75)) were entered in the study. No significant difference was found between the two groups, with the geometric mean (range) for serum E2 (x 10^{-12}mol/L) with 16 days administration of anastrozole being 2.7 (1.5-4.9) in the Japanese females (22 cases) and 3.3 (1.5-5.3) in the Western women (23 cases). No significant difference was likewise found between the two groups for the trough blood level of anastrozole in the steady state. It was considered from these study findings that the serum E2 inhibitory effect and pharmacokinetics of anastrozole are virtually the same in Japanese and Western subjects.

6) Late Phase II study (Protocol No. 1033JP/0027)

A comparative study similar to the randomized comparative study on anastrozole and TAM in primary endocrine therapy for post-menopausal progressive or recurrent breast cancer conducted from XXX(mth) XXX (yr) in Europe (Protocol No. 1033IL/0027, total cases 668) was undertaken as a bridging study in Japan from XXX(mth) XXX(yr). It looked at recurrent cases 12 or more months on since completing postoperative endocrinotherapy and progressive and recurrent cases who had not undergone endocrinotherapy. As regards hormone receptors, it looked at cases in whom estrogen or progesterone receptors in the primary focus or metastatic focus were positive or unknown. 11 cases were allocated to the anastrozole group and 20 to the TAM group. The success rates were anastrozole group: 45.5% (5/11cases) and TAM group: 35.0% (7/20 cases).

B) Details of evaluation by Evaluation Center

The investigations undertaken by the Evaluation Center were mainly in the following areas:

[Clinical ranking of anastrozole]

1) Ranking of anastrozole for post-menopausal advanced and recurrent breast cancer

It is currently often the case that the anti-estrogen agent TAM is used as primary therapy in endocrinotherapy for recurrent breast cancer and synthetic luteal hormone agents as secondary therapy in cases who have failed to respond to primary therapy or in cases of re-deterioration after completing the therapy (N Engl J Med 339:974, 1998). The Evaluation Center asked the applicant about the therapeutic ranking of aromatase inhibitors such as anastrozole in endocrinotherapy for post-menopausal advanced and recurrent breast cancer.

Aromatase inhibitors were developed with the aim of inhibiting tumour growth by blocking the formation of estrogen itself and aminoglutethimide began to be used clinically in the early 1980s (Br J Cancer 47:621, 1983). However, as the selectivity of aminoglutethimide for aromatase was poor and adrenocorticoid supplements were needed, more selective aromatase inhibitors were sought and fadrozole was developed as a result (Cancer Res 48:1998).

The degree of serum estradiol inhibition at the recommended clinical dose levels is respectively 80% for anastrozole and 63% for aminoglutethimide. (Br J Cancer 47:621, 1983) and 59% with fadrozole (Cancer Res 50:1381, 1990), suggesting high levels of serum E2 inhibition response with anastrozole.

In order to confirm the efficacy of anastrozole as secondary endocrinotherapy for post-menopausal breast cancer, randomized comparative studies with the synthetic luteal hormone agent megestrol acetate were conducted overseas (Protocol No. 1033IL/0004; Publication: Eur J Cancer 32A:404, 1996, Protocol No. 1033IL/0005; Publication: Cancer 79:730, 1997 and Publication: Cancer 83:1142, 1998, Cancer 85:1010, 1999 which combined the results of these two studies). These looked at cases of recurrence during postoperative endocrinotherapy lasting 6 months or more, cases relapsing within 12 months of the completion thereof, and progressive and recurrent cases resistant to primary endocrinotherapy. As regards hormone receptors, they

looked at cases in whom estrogen or progesterone receptors in the primary or metastatic lesion were positive or unknown. The success rates, deterioration-free median survival time and median survival time were respectively anastrozole 1mg/day (263 cases): 12.5%, 4.8 months and 26.7 months; anastrozole 10 mg/day (248 cases): 12.5%, 5.3 months and 25.5 months; megestrol acetate (253 cases): 12.2%, 4.6 months and 22.5 months. Whilst no statistically significant difference was found between the three groups in respect of success rate and deterioration-free median survival time, median survival in the anastrozole 1mg group was significantly longer than in the megestrol acetate group but there was no significant difference between the anastrozole 10mg group and megestrol acetate group. The frequency of adverse events manifested during and up to 2 weeks after the completion of the course of drug administration was 78% in the 1mg anastrozole group, 82% in the 10mg anastrozole group and 84% in the megestrol acetate group. The findings of these studies proved that anastrozole was in no way inferior to the existing megestrol acetate in its efficacy and safety as a secondary endocrinotherapy for post-menopausal breast cancer.

Next, randomized comparative studies on anastrozole and TAM the standard drug for primary endocrinotherapy in post-menopausal breast cancer were conducted overseas and in Japan (1033IL/JP0027; 1033IL/0027, 1033IL/0030). These looked at recurrent cases 12 months or more after the end of postoperative endocrinotherapy, or cases not treated by endocrinotherapy for progression or relapse. As regards hormone receptors, they dealt with cases in whom estrogen or progesterone receptors in the primary or metastatic lesions were positive or unknown. Upon analyzing the findings for 668 cases in Europe and 31 cases in Japan, the success rates and deterioration-free median survival time were respectively 33.3% and 251 days in the anastrozole 1mg group (351 cases) and 32.8% and 252 days in the TAM group (348 cases) and anastrozole provided efficacy in terms of success rate and deterioration-free median survival time at least equivalent to TAM. The frequency of adverse events manifested during and up to 2 weeks after the completion of the course of drug administration was 71.8% in the anastrozole 1mg group and 75.6% in the TAM group. In a similar study conducted in North America (Protocol No. 1033IL/0030), the success rates and deterioration-free median survival time were respectively 21.1% and 338 days in the anastrozole 1mg group (171 cases) and 17.0% and 170 days in the TAM group (182

cases), indicating efficacy with anastrozole at least equivalent to TAM and deterioration-free survival time being significantly longer in the anastrozole group. The frequency of adverse events was 97.6% in the 1mg anastrozole group, 94.0% in the 10mg anastrozole group and 84% in the megestrol acetate group. In the European study, 44.6% of the cases had been hormone receptor positive and the presence of hormone receptors had been unknown in 55.1%. In the North American study on the other hand, 88.7% of the cases had been hormone receptor-positive and the presence of hormone receptors had been unknown in 11.3%. The difference in the European and American study results may be considered to have come about as a result of differences in the background characteristics of the cases and in particular the presence or otherwise of hormone receptors.

In view of the above study results, the applicant responded that anastrozole would seem to be a drug providing efficacy and safety which could rank it as a first line choice in standard therapy in endocrinotherapy for post-menopausal progressive or recurrent breast cancer and the Evaluation Center accepted this.

2) Use of anastrozole for postoperative adjuvant endocrinotherapy in post-menopausal cases

The Evaluation Center asked the applicant about the use of anastrozole as postoperative adjuvant endocrinotherapy in post-menopausal breast cancer cases.

The applicant responded that TAM is widely used in post-menopausal patients for adjuvant endocrinotherapy postoperatively in breast cancer (N Engl J Med 339:1609, 1998). It is reported that TAM stimulates the endometrium by its estrogen-like action and the frequency of endometrial carcinoma consequently rises with long-term use (J Natl Cancer Inst 86:527, 1994). Aromatase inhibitors such as anastrozole have a different mechanism of action from TAM and there seems to be little possibility of them affecting the endometrium ((Drugs 58:233, 1999), and they are considered to suitable for postoperative endocrinotherapy requiring long term administration. It would also seem that anastrozole which has been suggested to be at least as effective and safe as TAM for progressive and recurrent cases could be a primary candidate for use in postoperative adjuvant endocrinotherapy. A clinical study on anastrozole in postoperative adjuvant endocrinotherapy is currently ongoing overseas (Protocol No.

IL 0029, randomized comparative study with 3 groups: anastrozole, TAM, anastrozole + TAM; 9200 cases approx.). A randomized comparative study on anastrozole and TAM on pre- and post-operative adjuvant therapy in operable post-menopausal cases is currently being planned with a common protocol for Japan and overseas. It is intended to assemble data on the long term use of anastrozole in Japan in this study. The efficacy and safety of anastrozole as postoperative adjuvant endocrinotherapy in post-menopausal breast cancer is currently not proven but the applicant believes that this will be verified by the results of the above clinical studies.

The Evaluation Center judged that the efficacy and safety of the long term use of anastrozole have currently not been established for postoperative adjuvant endocrinotherapy in post-menopausal breast cancer. It may be considered that the ranking of anastrozole in postoperative endocrinotherapy will be verified from the comparative studies on anastrozole and TAM in postoperative endocrinotherapy currently being conducted or planned by the applicant.

[Recommended clinical dose of anastrozole]

The Evaluation Center asked the applicant about the validity of setting the recommended clinical dose of anastrozole at 1 mg/day.

In a foreign study in healthy post-menopausal females (Protocol No. IL0009), serum E2 was below the detection limit (3 x 10^{-12}mol/L) after 14 days administration of a daily dose of 0.5mg and 1mg anastrozole in respectively 1/6 cases and 5/7 cases. Moreover, in a foreign study in post-menopausal breast cancer patients (Protocol No. 1033US/0003: Publication: J Steroid Biochem Mol Biol 59:439, 1996), the degree of decrease in serum E2 with 14 days administration of anastrozole at daily doses of 5 mg and 10 mg was about the same as with 1 mg/day. Furthermore, in a randomized comparative study on anastrozole and megestrol acetate conducted overseas (Protocol No. 1033IL/0004; Publication: Eur J Cancer 32A:404, 1996; Protocol No. 1033IL/0005 ; Publication: Cancer 79:730, 1997), the antitumour response with daily doses of 1 mg and 10 mg anastrozole had been 12.5% in the 1mg group (263 cases) and 12.5% in the 10mg group (248 cases) and it was judged that no enhancement of the antitumour response could be expected by increasing the dose of anastrozole to 10 mg.

In a Japanese study in healthy post-menopausal females (A-15-12), serum E2 (mean, x 10^{-12}-mol/L) before and after 14 days administration of 0.5 mg/day and 1 mg/day anastrozole had been respectively 35.2 ± 16.4 and 6.0 ± 3.5 in the 0.5mg group, and 25.3 ± 13.5 and 4.6 ± 2.3 in the 1mg group and serum E2 was reduced with statistical significance in the 1 mg group ($p=0.016$). An early Japanese Phase II study in post-menopausal breast cancer cases (A-15-21) gave success rates of respectively 2.8% (1/36) and 20.6% (7/34) at 12 weeks treatment with 0.5 mg/day and 1 mg/day anastrozole and the success rates at the time of the final evaluations at the end of the long term study were 0.5mg group 27.8% (10/36) in the 0.5 mg group and 1mg group 41.2% (14/34) in the 1 mg group. Adverse events encountered during this study as subjective and objective adventitious symptoms (grade; Japan Cancer Therapy Association 'Descriptions of adverse reactions, 1986') comprised 18 episodes in 36 cases in the 0.5mg group (grade 3: 1 case - chest wall pain believed to be associated with progression of the primary disease), 17 episodes in 34 cases in the 1 mg group (grade 3: 1 case - cervical pain thought due to lymph node metastases from primary disease; grade 4: 1 case (dyspnoea thought due to the appearance of new lesions) and

as abnormal variations in laboratory values (grade: adverse reaction criteria of Japan Clinical Oncology Group (JCOG)), there were 82 episodes in 36 cases in the 0.5 mg group (grade 3: 2 episodes) and 83 episodes in 34 cases in the 1 mg group (grade 3: 3 episodes), but the details and severity of adverse events were of a similar degree in both groups.

The applicant therefore replied that in the light of the above study results, the minimum dose providing the maximum reduction in the level of E2 in the blood was 1 mg and that as no enhancement of antitumour response had been noted when the dose had been increased beyond this, they had set the recommended clinical dose of anastrozole at 1 mg.

The Evaluation Center accepted this.

[Japanese and foreign bridging studies]

The Evaluation Center asked the applicant about the course and validity of the Japanese bridging study in the light of the foreign study (pharmacology study in healthy post-menopausal females; Protocol No. 1033IL/0035; Publication: Cancer Chemother Pharmacol 46:35, 2000) and the late Phase II study in post-menopausal breast cancer patients (1033JP/0027).

Comparative studies with megestrol acetate were already being conducted when the clinical development of anastrozole commenced in Japan, (1033IL/0004; Publication: Eur J Cancer 32A:404, 1996; 1033IL/0005 ; Publication: Cancer 79:730, 1997) and therefore 1 mg/day which was the low dose in the foreign comparative study was selected as the initial dose for the Japanese Phase I study (A-15-11). Almost the same antitumour response was noted at daily dose levels of 1-10 mg in post-menopausal breast cancer as a result of the Japanese Phase I study (looking at previously treated post-menopausal progressive or recurrent breast cancer patients; successful cases 1mg: 2/6 cases, 5mg: 2/6cases, 10mg: 2/8 cases). However, as no information had been obtained about antitumour response or decreases in blood E2 suggestive of this for daily dose levels of less than 1 mg anastrozole, a study was then undertaken to investigate decreases in blood E2 levels with 0.5 mg/day and 1 mg/day anastrozole in healthy post-menopausal females (A-15-12). It was consequently suggested that the decreases in E2 levels were more marked in the 1 mg group than the 0.5mg group. However, as it was considered that some degree of antitumour response could be expected even with the decreased E2 levels achieved in the 0.5 mg group, antitumour response was investigated in the early Phase II study (A-15-21) at daily doses of 0.5 mg and 1 mg anastrozole. The recommended clinical dose of anastrozole was consequently judged to be 1 mg/day. At the time when the Japanese early Phase II study had been completed, anastrozole had already been approved in the US and Europe as a secondary endocrinotherapeutic agent for post-menopausal progressive and recurrent breast cancer at a recommended clinical dose of 1 mg/day and the recommended clinical dose in Japan and overseas was the same.

A retrospective investigation was carried out based on the Japanese studies in post-menopausal breast cancer patients (A-15-11, A-15-21) and in healthy post-menopausal females (A-15-12) and the foreign studies on pharmacodynamic effect in

post-menopausal breast cancer patients (1033US/0003; Publication: J Steroid Biochem Mol Biol 59:439, 1996; 1033IL/0022) and pharmacokinetic studies in healthy post-menopausal females (IL0019; IL0009). Four things were suggested from this, namely that:

① pharmacokinetic linearity was suggested in both Western and Japanese subjects and the pharmacokinetic parameters were similar;

② no difference in pharmacodynamic effect (inhibition of blood E2 level) and dose-response to anastrozole was noted in healthy Western and Japanese subjects;

③ the recommended clinical dose of anastrozole is the same in Japan, Europe and the US at 1 mg/day;

④ there has been judged to be no difference in anastrozole tolerability between Western and Japanese subjects in healthy subjects and breast cancer patients. It is thus predicted that there will be no ethnic differences in the pharmacokinetics, efficacy and safety of anastrozole.

Therefore for the development of anastrozole in Japan, in the light of the International Conference on Harmonization (ICH) "Guidance on racial factors to be considered when accepting foreign clinical data (E5: *Iyakushin* 672, 11 August 1998)", it was decided on XXX(mth) XXX(yr) to verify efficacy by conducting a study in Japan (total 31 cases) similar to the randomized comparative study on anastrozole and TAM for primary endocrinotherapy in post-menopausal progressive or recurrent breast cancer being conducted at that time in the US and Europe (1033IL/0027, European study: total cases 668, commenced XXX(mth) XXX(yr), ceased case enrolment XXX(mth) XXX(yr); 1033IL/0030 US study: total cases 353, commenced XXX(mth) XXX(yr) (Japanese late Phase II study 1033JP/0027). The number of cases in Japan was selected as follows:

① if the point estimate for the success rate in Japanese breast cancer patients were 10% or less, it would be difficult to claim same the degree of efficacy between Japanese and Westerners, but if the true success rate in the anastrozole group were, say, 30%, the probability for such a result would be 0.035 if there were 15 cases, and

② if the point estimate for the success rate were 20% or more, this could be regarded as a result supporting a similar degree of efficacy between Japanese and if the

true success rate in the anastrozole group were 30%, the probability for such a result would be 0.873 and it was felt that with 15 cases, there would be a fairly high chance of being able to judge efficacy between Japanese and Westerners as being of the same degree. It was therefore considered reasonable to set a planned number of 15 cases for the anastrozole group and a total of 30 for the study. The number of cases actually entered into the Japanese study was biased with 11 cases in the anastrozole group and 20 in the TAM group, but as stratified allocation depending on the state of metastases had been undertaken at each institution, the bias in the number of cases between the groups may be thought to have arisen by chance. The actual success rate in this therapeutic group was 45.5% (5/11 cases). Supposing 4 cases had been added to make 15 cases, even if all 4 had been unsuccessful, the success rate would still have been 33.3% (5/15 cases) and the conclusion of a similar degree of efficacy in Japanese and Western patients would be unchanged. The bias seen in the present number of cases was therefore considered not to have had any major effect on the evaluation of the results.

As the Japanese comparative study (1033JP/0027) was conducted in so few cases, it was decided to undertake a bridging study on clinical pharmacology in healthy post-menopausal Japanese and Western females in order to verify prospectively the fact that the pharmacokinetics and pharmacodynamics (serum E inhibitory activity) with 16 days administration of 1 mg/day anastrozole are equivalent (1033IL/0035; Publication: Cancer Chemother Pharmacol 46: 35, 2000, 24 Japanese and 24 Western cases) and provide data supporting the results of the said comparative study. It was decided that this should be a bridging study on clinical pharmacology not in patients but in post-menopausal healthy females for the reasons that:

① the degree of plasma E2 inhibition following the administration of 1 mg/day of anastrozole had been virtually the same in the study in post-menopausal healthy females (A-15-12) and the study in post-menopausal breast cancer patients (A-15-11) in Japan. In Europe and America, the total serum estrogen concentration in post-menopausal breast cancer patients and healthy females had been reported to be almost at the same levels (Lancet 2:1100, 1976) and it would appear that post-menopausal breast cancer patients and post-menopausal healthy females have a very similar endocrine environment;

② clinical studies on anastrozole in post-menopausal healthy females and post-menopausal breast cancer patients have already been conducted in Japan and there were considered to be no particular safety problems with administering anastrozole for 16 days to post-menopausal healthy females; and

③ as plasma E2 concentration the assay limit after the administration of anastrozole, in order properly to compare the pharmacological activity of the drug (inhibition of blood E2 level) in Japanese and Western subjects, it was felt necessary to control variations in the concentration measurements as much as possible and it was hence decided to measure specimens from one location. As it would also longer to enrol subjects for a study in breast cancer patients than healthy subjects, it was considered that it would be difficult to have all the specimens available at the same time.

In the studies in Japanese and Western post-menopausal healthy females (A-15-12) (1033IL/0019), the pharmacokinetic parameters upon giving a single dose of 1 mg anastrozole in a day were much the same in both subject groups (Japanese (6 cases) and Westerners (15 cases): Tmax (h) 1.3 ± 0.2 and 1.3 ± 0.1, Cmax (ng/mL) 17.8 ± 1.0 and 18.6 ± 0.8, $AUC_{0\text{-inf}}$ (μg.h/mL) 1.04 ± 0.12 and 0.93 ± 0.06, t1/2 (h) 56.3 ± 4.5 and 51.0 ± 3.5). Moreover, in the bridging study on clinical pharmacology (1033IL/0035; Publication: Cancer Chemother Pharmacol 46: 35, 2000), no statistical difference had been noted in the minimum plasma concentration of anastrozole (ng/mL) (mean values (range) Japanese (22 cases) 30.4 (15.9 – 54.0), Westerners (23 cases) 25.7 (12.3 – 53.7), p=0.094). Further, serum E2 (x 10^{-12} mol/L) and serum E1S (x 10 -12 mol/L) following the administration of anastrozole for 16 days were similar in degree at respectively Japanese (22 cases, mean (range) 2.7 (1.5 – 4.9) and 39.5 (10.0 – 227.0), Westerners (23 cases, mean (range) 3.3 (1.5 – 5.3) and 32.0 (10.0 – 85.0). No statistically significant difference was found between the two groups for serum E2 concentration (p=0.102) and serum E1S concentration (p=0.475). These findings suggested that the pharmacokinetics and anti-estrogen action of anastrozole are similar same Japanese and Western post-menopausal healthy females.

The success rates in the randomized comparative studies on anastrozole (1 mg/day) and TAM as primary endocrinotherapy in post-menopausal progressive and recurrent breast cancer (1033JP/0027) in Japan were anastrozole group 45.5%

(5/11cases) and TAM group 35.0% (7/20 cases), and overseas (1033IL/0027) were anastrozole group 33.5% (105/313 cases) and TAM group 32.0% (95/297 cases), suggesting that the efficacy of anastrozole is of much the same degree in Japanese and Western patients.

In view of the above study findings, it was considered that:

① the endocrine environment would seem to be very similar in post-menopausal healthy females and post-menopausal breast cancer patients (A-15-11, A-15-12, A-15-21;Lancet 2: 1100, 1976);

② the pharmacokinetics and estrogen-inhibiting activity of anastrozole in Japanese and Western post-menopausal healthy females was suggested to be about the same;

③ from ① and ②, the pharmacokinetics and estrogen-inhibiting activity of anastrozole were inferred to be about the same in Japanese and Western cases of post-menopausal breast cancer; and

④ the efficacy of anastrozole was suggested to be of a similar degree in Japanese and Western cases of post-menopausal breast cancer (1033JP/0027, 1033IL/0027).

The applicant replied that it would be reasonable to conclude that the efficacy of anastrozole in post-menopausal progressive and recurrent breast cancer would be of the same order in Japanese and Western patients. The applicant also said that as criteria which can define ethnic difference have not been established in respect of decisions on bridging, they investigated individual variations in blood E2 levels and if the ethnic difference was less than 1.5 times relative to serum E2 in Western breast cancer patients (3 pmol/L), there could be judged to be no clinically meaningful ethnic difference and based on this criterion, they had set the number of cases for the bridging study in healthy subjects.

The Evaluation Center accepted this.

From the data submitted on this occasion, the Evaluation Center considers the complete clinical data package for anastrozole to comprise:

Foreign data: pharmacokinetic studies in post-menopausal healthy females (IL0019) (IL0009), pharmacodynamic investigative studies in post-menopausal breast

cancer patients (1033US/0003; Publication: J Steroid Biochem Mol Biol 59:439, 1996)(1033IL/0022), randomized comparative study with TAM in primary endocrinotherapy for post-menopausal progressive and recurrent breast cancer patients (1033IL/0027);

Japanese data: Phase I study in post-menopausal breast cancer patients (A-15-11), clinical pharmacology study in post-menopausal healthy females (A-15-12), early Phase II study and long-term study in post-menopausal breast cancer patients, and

Bridging studies: Clinical pharmacology study in Caucasian and Japanese post-menopausal healthy females (1033IL/0035: Publication: Cancer Chemother Pharmacol 46: 35, 2000), Japanese late Phase II study in post-menopausal breast cancer patients (comparative study the same as foreign study with TAM to confirm potency (1033IL/0027))

From the results of these studies:

① it was suggested that the pharmacokinetics and estrogen-inhibiting activity of anastrozole were equivalent in Japanese and Western post-menopausal healthy females;

② it had been inferred that the pharmacokinetics and estrogen-inhibiting activity of anastrozole would also be equivalent in Japanese and Western post-menopausal breast cancer cases:

③ the recommended clinical dose of anastrozole is the same in Europe, the US and Japan;

④ it was suggested that the efficacy of anastrozole would be virtually the same in Japanese and Western post-menopausal breast cancer patients and ⑤ it was suggested that there is no difference between Japan and overseas in the adverse event profile found for anastrozole, and in view of these facts, the Evaluation Center determined that a complete clinical data package on anastrozole had been assembled. However, in view of the fact that it had been necessary to measure specimens from one position in order to control scatter in the measurements of blood E2, which constituted the index of the pharmacological effect of anastrozole, the Evaluation Center determined that the study to verify the pharmacokinetics and pharmacological action of anastrozole as

bridging between the Japanese and foreign situations should have been conducted in post-menopausal breast cancer patients instead of post-menopausal healthy females.

The Evaluation Center also asked the applicant to explain the comparability of blood levels of anastrozole in the bridging study on clinical pharmacology and the reason for comparing the minimum plasma concentration (Cmin) as the appropriate parameter.

The applicant replied that the study design, dose levels and conditions for the measurement of plasma concentrations etc. in this study had been the same and that although mean Caucasian body weight is 1.2 times that of Japanese subjects, such weight difference is seen in resident populations typical of both regions and the validity of comparing plasma concentrations in Japanese and Caucasians in this study seems undeniable, they had judged it should be possible to compare the plasma concentrations of anastrozole in Japanese and Caucasians. Furthermore, the reason for comparing Cmin of anastrozole was that a comparison of existing data had suggested that plasma anastrozole following a single oral dose in Japanese and foreign subjects followed a similar course, and as the accumulation factor for anastrozole in the plasma observed with multiple doses closely matched the values predicted from the single dose results, it was felt that plasma anastrozole with multiple dose administration could be estimated from the single dose results, and AUCτ (τ: dose interval) in the steady state in Japanese and foreign subjects were anticipated to be the same. Therefore, they had decided that by confirming that there was no difference in Cmin of anastrozole, they could deduce that the course of anastrozole concentrations in the plasma was similar.

The Evaluation Center accepted this argument.

[Safety of anastrozole]

1) Difference in frequency, content and severity of adverse events with anastrozole noted during Japanese and foreign comparative studies

The Evaluation Center asked the applicant whether or not there had been any particularly noteworthy difference in the frequency, content and severity of the adverse events noted in the two therapeutic groups during the Japanese and foreign randomized comparative studies on anastrozole and TAM in post-menopausal progressive and recurrent breast cancer (1033JP/0027), (1033IL/0027).

The severity classification for adverse events encountered during the Japanese and foreign comparative studies was classified as mild: adverse events manifested but tolerable and controllable, moderate: of a degree limiting ordinary activity and severe: of a degree making work or ordinary activity impossible. The frequency of adverse events was as follows:

Japanese study - anastrozole group 15 episodes in 11 cases (of which one episode was moderate); TAM group 23 episodes in 20 cases (of which 4 episodes were moderate)

Foreign study: anastrozole group 948 episodes in 336 cases (of which 263 episodes were moderate and 66 severe), TAM group 983 episodes in 329 cases (of which 279 episodes were moderate and 77 severe). In the Japanese clinical studies, the majority of adverse events in both groups were mild and no serious adverse events were noted. Overseas, there were more moderate and severe adverse events but the majority of these comprised flushing which was considered to be attributable to the pharmacological activity of the drug. Likewise, no adverse events with a high frequency specifically amongst Japanese or Westerners nor serious adverse events were observed. The applicant stated that the adverse events observed with anastrozole may be thought not to differ greatly in Japanese and Western subjects.

The Evaluation Center accepted this.

2) Effect of anastrozole on the endometrium

The Evaluation Center asked the applicant about the effects of anastrozole on the endometrium compared to TAM.

The applicant responded that an investigation of endometrial weight giving anastrozole for three days to juvenile female rats (0.02-1 mg/kg/day) had indicated no

endometrial hyperplasia with short term administration. In a two-year carcinogenicity study in mice and rats, no increase in the frequency of uterine tumours had been noted up to 50 mg/kg/day anastrozole in mice, but in the rat 25mg/kg/day group, an increased frequency of cystic hyperplasia and interstitial polyps was noted. The findings in rats were that the level of estrogen decreased due to the aromatase inhibitor anastrozole but in the rat, it was subject to the influence of endocrinal system feedback and rises in gonadotropin were seen. As a result, it seems that an endometrial growth effect due to changes in the kinetics of gonad hormones secreted from the ovaries had come about. As no such sexual hormone feedback is found in post-menopausal females, it was inferred that the uterine changes noted in rats would not represent any clinical problem.

TAM on the other hand, is an anti-estrogen agent but is believed to exhibit estrogen-like action on the endometrium (J Natl Cancer Inst 87: 746, 1995) and increased adverse events relating to the uterus (endometrial hyperplasia, endometrial polyps etc.) have been reported with the long term use thereof (treatment period 2-47 months) by post-menopausal breast cancer patients (Obstet Gynecol 81:660, 1993, Breast Cancer Res Treat 26:101, 1993, Breast Cancer Res Treat 53: 255, 1999).

In the Japanese and foreign randomized comparative studies with anastrozole (347 cases) and TAM (349 cases) in post-menopausal breast cancer ((1033JP/0027), (1033IL/0027), one case each of endometrial hyperplasia was found in each treatment group.

From the results of the non-clinical studies and mechanism of action, the effects of anastrozole on the uterus may be considered to be less than with TAM even in long term use, but actions on the endometrium with long term treatment are currently being investigated in a foreign clinical study on postoperative adjuvant therapy with anastrozole.

The Evaluation Center accepted this response.

3) Effects of anastrozole on coagulation-fibrinolysis system

In the Japanese and foreign randomized comparative studies with anastrozole and TAM in post-menopausal breast cancer (1033JP/0027; 1033IL/0027; 1033IL/0030), no statistically significant differences were noted in the incidence of thrombosis for which causality by the drug could not be ruled out, this being 0.77%

(4/517 cases) in the anastrozole group and 1.51% (8/531 cases) in the TAM group. As the appearance of thrombosis had been noted in the anastrozole group too, the Evaluation Center asked the applicant about the need for such information to be reflected in the package insert, as well discussing as the possibility of thrombosis in man in terms of its mechanism of action.

The applicant replied that action on the blood coagulation fibrinolysis system (activated partial thromboplastin time, prothrombin time and euglobulin lysis time) had been investigated giving rats 1 and 10 mg/kg anastrozole but no effects had been noted. In a one-month multiple dose study in rats, a slight shortening of the prothrombin time had been noted at 25 mg/kg/day anastrozole, but no signs suggesting effects on the coagulation system had been obtained in a multiple dose study up to 12 months with anastrozole (18 mg/kg) in dogs.

In a single dose study on anastrozole in foreign healthy males (0.1-60 mg/dose) (1033HQ/0001) and an investigation of anastrozole in post-menopausal healthy females given anastrozole (3 mg/dose) on the first day and the 7 days from the 4th to the 10th day (8 doses in total), no statistically significant differences had been found in the anastrozole and placebo groups for the platelet count, prothrombin time, activated partial thromboplastin time in healthy subjects.

Thrombosis and embolism-related adverse events in the Japanese and foreign randomized comparative studies with anastrozole and TAM in post-menopausal breast cancer had occurred in 4.4% (23/517 cases) in the anastrozole group and 7.3% (39/531 cases) in the TAM group. The median presentation period (range) and median age at presentation (range) had been 92 days (18-553) and 79 years (57-89) in the anastrozole group and 85 days (7-774) and 71 years (50-91) in the TAM group. No consistent trend had been found in the age etc. at the time of thrombosis presentation in both groups. In the foreign randomized comparative studies on anastrozole and megestrol acetate in post-menopausal breast cancer (1033 IL/0004 ; Publication: Eur J Cancer 32A:404, 1996), (1033 IL/0005; Publication: Cancer 79:730, 1997), the incidence of thrombosis held to be adverse events was 3.4% (9/262 cases) in the anastrozole 1mg group and 1.6% (4/264 cases) in the 10mg group. and 4.7% (12/253 cases) in the megestrol acetate group, with no significant difference between the three groups.

In view of the findings of the non-clinical and clinical studies, any effects of anastrozole on the coagulation system are unclear and there was considered to be no reason to give a warning about increased incidence of thrombosis due to the administration of the drug. However, the Evaluation Center felt that although no causal relationship between anastrozole and thrombo-embolism had been established, thrombo-embolism had in fact been seen in the clinical studies and the possibility that anastrozole affects the blood coagulation and fibrinolysis system cannot be fully ruled out in the light of current knowledge. With the aim of ensuring greater safety, it therefore instructed the applicant to state in the 'Other warnings' in the Precautions and Warnings that "Whilst any causality by anastrozole is unclear, thrombo-embolism has been reported in clinical studies". The applicant also responded that they would continue to gather more information about the presentation of thrombosis during the long term use of anastrozole.

The Evaluation Center accepted this.

4) Arthralgia due to anastrozole

In the Japanese and foreign randomized comparative studies with anastrozole and TAM in post-menopausal breast cancer ((1033JP/0027), (1033IL/0027), (1033 IL/0030), a higher frequency of arthralgia (including arthritis and arthropathy) as adverse events had been noted in the anastrozole group at 10.6% (61 episodes in 55 cases) than in the TAM group 5.5% (29 episodes in 29 cases). The Evaluation Center therefore asked the applicant about the mechanism whereby arthralgia is induced by anastrozole.

The applicant replied that no changes suggesting joint abnormalities or other findings suggesting inflammation of the joints had been noted in the multiple dose studies on anastrozole in dogs and rats. In the present comparative studies, more joint-related adverse events had occurred than in the TAM group and some causality by anastrozole could be suspected but the mechanism involved was unclear. The arthralgia found in the anastrozole in the comparative studies had not been serious. Looking at the joint-related (e.g. arthralgia) adverse events noted in randomized comparative studies on other aromatase inhibitors with megestrol acetate control in post-menopausal breast cancer, the incidence thereof tended to be higher with the

aromatase inhibitor than in the control group, viz. with retrosol (retrosol 0.5mg group 8.5% (16/188 cases) 2.5 mg group 13.2% (23/174 cases), megestrol acetate group 7.9% (15/189), J Clin Oncol 16:453, 1998) and borosol (borosol group 13.3% (30/195 cases), megestrol acetate group 7.5% (17/198 cases), J Clin Oncol 17:52, 1999). None of the arthralgia found in these studies had been serious. However, it was suggested that arthralgia is an adverse event characteristic to aromatase inhibitors including anastrozole.

The frequency of arthralgia in the comparative studies on anastrozole with TAM and megestrol acetate tended to be higher than with the control drug and it is suggested that there is a possibility of some kind of arthralgia being induced by the use of anastrozole. Amongst the 21 evaluable cases from 35 reported with spontaneous adverse events for joint-related symptoms following the commercial launch of anastrozole, 7 had been serious (2 cases requiring admission, 5 cases leading to functional failure). The Evaluation Center therefore judged that the frequency and degree of joint-related adverse events associated with the use of anastrozole should be gathered from the clinical studies on postoperative adjuvant therapy etc. currently in progress and the safety of anastrozole should be investigated further.

[Text in Precautions and Warnings]

1) Long term use of anastrozole

As the efficacy and safety of the long term use of anastrozole in postoperative adjuvant therapy is not proven, the Evaluation Center asked the applicant about the need to mention this in the Precautions and Warnings.

The applicant replied that text stating that "The efficacy and safety of anastrozole in postoperative adjuvant therapy is not proven" would be added to the section on important basic precautions and the Evaluation Center accepted this.

2) Use of anastrozole in cases with hepatic or renal impairment

As effects on the liver and kidney had been noted in the toxicity studies on anastrozole in rats and dogs and abnormal variations in laboratory values relating to the liver and kidney had been found in the clinical studies, the Evaluation Center asked the applicant about the safety of anastrozole in cases with hepatic or renal impairment.

In a study comparing the pharmacokinetics with a single 1 mg dose of anastrozole in 8 cases with cirrhosis of the liver with 8 healthy subjects, (Protocol No. IL0014), Cmax and AUC of anastrozole increased respectively 25% and 29% and a statistically significant difference in Cmax was seen between the two groups. The half life of anastrozole in the blood tended to be longer in the hepatically impaired cases but no significant difference was found between the two groups. There were no problems with tolerability and it was concluded that no dose adjustment was needed.

In a study comparing the pharmacokinetics of a single 10 mg dose of anastrozole in 7 cases with mild to moderate renal impairment (creatinine clearance 10-30 mL/min) with 7 healthy subjects, (Protocol No. IL0018), Cmax and AUC in the renally impaired cases was 83% and 93% of those in the healthy subjects but no significant differences were found between the two groups. The half life of anastrozole in the blood was about the same in both groups. The hepatic or renal impairment due to anastrozole found in the clinical studies was transient and nothing serious was noted. Glomerular nephritis was found in one case using anastrozole (Protocol No. IL0027) but this was thought to have been due to paratumour syndrome.

In view of the above, there seemed to be no need to contraindicate or adjust the dose of anastrozole for cases with mild to moderate hepatic or renal impairment. However, as the safety of anastrozole in cases with severe hepatic or renal impairment is not proven at the present point in time, the applicant will state in the Precautions and Warnings that it should be administered with caution to cases with severe hepatic or renal impairment. The Evaluation Center accepted this.

3. Result of Data Compliance Survey by Kiko and Evaluation Center Decision

I) Decision by Evaluation Center on compliance form survey result

As a result of the inspection conducted by Kiko with the form prescribed in Article 14-4 of the Pharmaceutical Affairs Law, despite some non-compliance (deviations from trial protocol for some of the clinical study results etc.), the Evaluation Center had judged in respect of the reports thereon that there was no obstacle to conducting a review based on the approval evaluation data.

II) Evaluation Center decision on GCP site inspection result

The GCP assessment gave a 'pass' result and it was judged that there was no obstacle to conducting the evaluation based on the approval dossier submitted.

4. Overall Evaluation

As a result of undertaking the investigations outlined above on the submitted data, the Evaluation Center judged that Arimidex may be approved for the application dosage and administration and uses in view of the following.

As the results of the Japanese and foreign clinical studies submitted on this occasion seemed to indicate that the pharmacokinetics and pharmacodynamic effect of Arimidex in Japanese and Western subjects were similar and that a dose-finding study in Japan had produced the same recommended clinical dose in Japan and overseas, it was considered that a complete clinical data package on anastrozole had been assembled and the Evaluation Center concluded that:

① The efficacy of anastrozole as endocrinotherapy for post-menopausal breast cancer is recognized,

② The safety of anastrozole for the application dosage and administration is assured.

Moreover, randomized comparative studies with anastrozole and TAM in pre- and post-operative adjuvant therapy in operable post-menopausal cases are currently being planned under a common protocol in Japan and overseas and it was felt that further information on the efficacy and safety of anastrozole would be forthcoming.

However, as the efficacy and safety of anastrozole used long-term as postoperative adjuvant therapy in post-menopausal breast cancer is not proven at the present point in time, the Evaluation Center judged that text stating that "The efficacy and safety of this agent in postoperative adjuvant therapy is not proven" should be included in the Precautions and Warnings so that caution is exercised in its use in postoperative adjuvant therapy until such time as information on its efficacy and safety has been assembled.