SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of . This scientific discussion has been updated until 30 June 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Targretin contains the new chemical entity bexarotene (INN), an anti-neoplastic retinoid. It is related to the other retinoids. It is indicated for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) patients refractory to at least one systemic treatment. The recommended initial dose is 300 mg/m^2/day, to be taken as a single dose with a meal.

The incidence of CTCL is approximately 1200 new patients annually in Europe with a prevalence of about 16,000. The term CTCL includes mycosis fungoides and Sézary syndrome. They usually manifest in the skin as a progressive disease, more common in men, age range usually 45-65 years. Extra cutaneous sites are involved later in the course of the disease. Sézary syndrome is an aggressive systemic variant of mycosis fungoides where there are abnormal circulating lymphocytes. Sézary cells are hyperchromatic mononuclear cells in the peripheral blood containing convoluted or ceribriform nuclei.

Current systemic therapy for CTCL includes interferon α, retinoids and PUVA therapy, either alone or in combination, and different monochemotherapy regimens. Radiotherapy and electron beam therapy have been employed for localised lesions. Photophoresis with oral metoxypsoralen and extracorporal irradiation of leukocytes and polychemotherapy regimens have been given for Sezary syndrome.

CTCL patients usually survive for many years after diagnosis, but there is a risk of secondary cutaneous malignancies, such as squamous cell carcinoma, because of the altered immunology caused by the disease or its treatment. The relative risk of skin cancers or melanoma is some 6-8 folds. Ulceration of CTCL with secondary infection is common and about half of the patients die from infection. The risk of infection is higher with immunosuppressive treatment.

Retinoids, such as etretinate and isotretinoin, have been used successfully to treat CTCL. They have been used both as sole agents and as part of combination therapy.

Bexarotene is a synthetic compound that exerts its biological action through selective binding and activation of the three retinoid X receptors (RXRs): RXRα, β, and γ. Once activated, these receptors function as transcription factors that regulate processes such as cellular differentiation and proliferation, apoptosis, and insulin sensitisation. The ability of the RXRs to form heterodimers with various receptor partners that are important in cellular function and in physiology indicates that the biological activities of bexarotene are more diverse than those of compounds that activate the retinoic acid receptors (RARs). In vitro, bexarotene inhibits the growth of tumour cell lines of haematopoietic and squamous cell origin. In vivo, bexarotene causes tumour regression in some animal models and prevents tumour induction in others. However, the exact mechanism of action of bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown.

2. Chemical, pharmaceutical and biological aspects

Composition

Targretin capsules are presented as off-white oblong soft gelatin capsules, imprinted with the word "Targretin" using blue ink and containing a suspension of 75 mg of micronised bexarotene in Macrogol 400. The capsule shell is made from gelatin, which is of animal origin. Gelatin complies with the Note for guidance on minimising the risk of Transmitting animal Spongiform Encephelopathy Agent.

Capsules are packaged in white 200-ml high-density polyethylene (HDPE) bottle with a white polypropylene child-resistant cap, and a tamper-evident foil inner-seal. Bottles are packaged in an outer cardboard container.

Active substance

The active substance bexarotene, supplied by Raylo Chemical Inc., is a new synthetic compound representing a sub-class of retinoids, but it is structurally distinct from the vitamin A derived retinoids. Its chemical name is 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8- tetrahydro-2-naphtalenyl)vinyl] benzene carboxylic acid.

The synthesis of bexarotene has evolved through two routes, which are not basically different. The second (route B) was more economic and more robust than the earlier route A and the impurity profile has been improved.
The first route (route A) was used for early pre-clinical studies and to produce the first lots for clinical trials.
Route B is the intended commercial route to manufacture the drug substance; Route B material has been used in the 6-month toxicology studies and for the majority of clinical studies.
Raylo manufactures the active substance at two facilities sites (Argyll Rd. and Clover Bar).
The equipment used for the bexarotene manufacturing process at the Argyll Road facility and the Clover Bar facility is equivalent and similar chemical and physical characteristics of drug substance issued from the two sites have been shown. The drug substance is prepared using synthetic transformations that are well precedented in the chemical literature.

The specifications contain all appropriate tests for identity, potency, purity and stability of the active substance. Bexarotene is identified by two methods: IR spectroscopy and HPLC.
The specifications for residual solvents that may be present are consistent with ICH guidance on residual solvents and therefore should not give rise to any toxicological problems.
The assay and determination of related substances are done using an isocratic HPLC.

Two identified impurities, have been routinely detected in bexarotene at levels greater than 0.1%. A further impurity was difficult to detect and although this impurity was present at trace levels (<0.1%) in many of stability study samples, it was not usually detected or reported. A limit of 0.2% has been specified.
The specifications for impurities are qualified by the 6-month rat toxicology study.

Particle size limits are consistent with the data of all available micronised bexarotene batches.

Batch analysis data were provided on seven batches (3 pilot and 4 production-scale) of active substance manufactured by route B and used in safety studies, clinical trials and stability studies. These data confirm the consistency and uniformity of the synthesis.

Stability studies of three representative commercial batches of micronised bexarotene have been carried out according to ICH storage conditions. Data observed for up two years at 25°C / 60% RH and for 6 months at 40°C/75 %RH justifies a re-test period of two years. The product should be stored at a temperature not exceeding 30°C.
Additional stability data performed at 5°C for 24 months and for 12 months at 30°C / 60%RH as well as photostability investigations confirmed the stability of bexarotene.
Nevertheless, bexarotene should be protected from extreme heat and from excessive light exposure.

Other ingredients

The excipients of the bulk suspension (Macrogol 400, polysorbate 20, povidone K-90, butylated hydroxyanisole) and the capsule shell (gelatin and titanium dioxide) comply with the corresponding PhEur monograph. The specifications for polysorbate 20 include an upper limit of NMT 1 ppm for ethylene oxide as additive specification to the PhEur. monograph.

Although the specifications of excipients relative to capsule shell (sorbitol special –glycerine blend and blue ink Colorcon) are limited, they have been found satisfactory. For the colorant FD&C Blue

N°2 aluminium lake (E132) used in the blue printing ink the compliance with the Directive78/25/EEC has been confirmed.

Product development and finished product

The final polyethylene glycol based formulation was selected after evaluation of protype formulations with respect to hydrophilic-lypophilic character of vehicle, viscosity of suspension, solubility of bexarotene in vehicle and bexarotene particle size.

A series of 10 small pilot scale batches (~25.000 capsules) were manufactured at R.P Scherer. Release data for these small batches showed consistent results for dissolution, content uniformity, BHT content and assay, with an RSD for content uniformity no greater than 2.0 %.
Eight scale-up batches including the three registration batches were manufactured using the production scale manufacturing process. Type of equipment used, main steps of manufacturing process are reported. The differences with the pilot scale are minor.
Release data showed similar satisfactory results to pilot scale batches.

The proposed commercial composition of Targretin capsule is essentially similar to the formulations used in the clinical trials.

The manufacturing process involves the preparation of a suspension of the active substance in the excipients, which is then encapsulated in soft gelatin.
The manufacturing equipment is described (class and subclass).
Appropriate in-process controls are in place.

A manufacturing process validation report is submitted for three consecutive full scale production batches manufactured with the commercial process parameters specifications (mixer speeds and times) validated during the additional mixing studies. The results of the validation studies are satisfactory.

Control testing of the finished product offers a full guarantee in terms of safety, efficacy and reproducibility of the process.

The control test and specifications for finished product are adequately drawn up. The identity is confirmed by IR-spectroscopy and high performance liquid chromatography. HPLC was also used for the assay and the detection of related substances.

The dissolution test is performed in a two–tier dissolution testing approach, with 0.005% of pancreatin present in the medium. As there is no evidence to suggest that the dissolution method is discriminatory with respect to particle size of the capsule fill suspension (complete dissolution of the bexarotene occurs in less than ten minutes when the fill suspension is added to the dissolution medium) the Marketing Authorisation Holder has included a release test of the bexarotene particle size distribution in the drug product, to ensure that this attribute is controlled in the finished product.
The limits for the bexarotene particle size distribution in the fill suspension are adequately justified.

The impurity limits in the finished product specification are justified by toxicology studies.

The limits for the microbial contamination are based on the requirements of the USP, but harmonisation of the Ph.Eur. With the USP with regard to microbiological quality has been realised with the acceptance of the step 4 documents for ICH Q6a.

Results from 3 commercial batches with printed capsules are presented. The results confirm satisfactory uniformity of the product at release and indicate reliable and consistent performance of the product in clinical use.

Stability of the product

The results from the stability studies indicate that the capsules exhibited satisfactory potency, purity and physical integrity. The physical appearance of the capsules and the dissolution data obtained show

no change during storage. The results support the proposed shelf-life of 2 years, as defined in the SPC. The Marketing Authorisation Holder has committed to provide stability data (both real and accelerated data) generated on the first three consecutive production batches of finished product (See section II.3,)

Discussion on chemical, pharmaceutical and biological aspects

In summary, the documentation of substances, materials, methods of production as well as the quality controls is sufficient to ensure a product of appropriate and consistent quality. Information has been provided in the dossier demonstrating that the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

3. Toxico-pharmacological aspects

Pharmacodynamics

In vitro studies

The activity of bexarotene has not been explored in models of CTCL, since no pre-clinical models exist. Therefore the exact mechanism of action of bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown. However, the following cell systems are known to respond to RAR-active ligands:

Promyelocytic leukaemia cell system

In the HL-60 promyelocytic leukaemia cell system bexarotene induced markers consistent with the induction of apoptosis, DNA laddering and morphological changes. At RXR/RAR-activating concentrations bexarotene was able to inhibit the growth and induce differentiation of the cells and was also capable of inducing differentiation of leukaemia cells from patients, including those with acute promyelocytic leukaemia (APL). When tested against the APL cell line NB4 (which harbours the same t (5:17) chromosomal translocation detected in the majority of APL patients) bexarotene at concentrations $\geq$ 1 μM was able to induce cell cycle arrest in G1 and to induce the expression of the granulocyte diffentiation antigen CD11b on the cell surface.

HBE Cells

Bexarotene inhibited transcription factor AP-1 (AP-1) activity in cultured human bronchial epithelial (HBE) cells. Other agents known to inhibit AP-1 activity also inhibited the expression of the differentiation markers. Bexarotene has been demonstrated to have anti-AP-1 activity mediated via RXRα. This effect may account for its ability to inhibit cellular proliferation.

Squamous cell carcinoma xenograft tumours in nude mice

9-*cis*-RA suppressed the differentiated squamous phenotype with the increased presence of basal tumour cells; bexarotene caused no change in the highly differentiated phenotype of the tumour. In addition, bexarotene inhibited the growth of two primary human HNSCC xenograft tumours grown in nude mice, but did not inhibit the growth of 1483 HNSCC xenograft tumours; bexarotene was not a potent antiproliferative agent in these cells.

Prostate cancer cell line (LNCaP)

Bexarotene was ineffective at inhibiting the growth of xenograft tumours derived from the human prostate cancer cell line or the transplantable Dunning prostate tumour in the rat.

Cultured AIDS-KS cells

Bexarotene (10^{-8} – 10^{-6} M) inhibited cellular proliferation in culture in a dose-dependent manner and similar to ATRA and RAR ligand. These data suggested that bexarotene may have inhibitory activity for AIDS-related KS cells in vivo.

Cultured breast cancer cells

Growth of the human oestrogen receptor (ER)-positive breast carcinoma cell line, T47D, was inhibited in a concentration dependent manner by bexarotene. Bexarotene and TAM appeared to be synergistic in the inhibition of the growth of these cells.

In vivo studies

Bexarotene inhibited the development of carcinogen-induced mammary carcinomas in the rat similar to tamoxifen (TAM). However, bexarotene did not induce significant changes in circulating levels of oestradiol, progesterone or prolactin. In addition, bexarotene and TAM appeared to be synergistic in this model. When bexarotene was added to the TAM regimen in animals with TAM-resistant mammary carcinomas, 94% of tumours had an objective response.

Pharmacodynamic drug interactions

When bexarotene or gemfibrozil was administered to rats, bifunctional enzyme (BE) and acyl-CoA oxidase RNAs were induced, and the combination of bexarotene and gemfibrozil led to greater induction.

General and safety pharmacology programme

Studies investigating cardiovascular and neuropharmacological parameters in rats were performed. Bexarotene administered to rats at 10, 30 and 60 mg/kg/day did not significantly affect mean arterial blood pressure or heart rate. Statistically significant changes were observed in two clotting parameters, but were not biologically important.

Hypertriglyceridaemia was seen after oral administration of bexarotene in a variety of animal models. Oral administration of bexarotene to rats increased the plasma levels of ApoA-I and HDL in the circulation. Induction of ApoA-I occurred at the transcriptional level.

The effects of bexarotene on plasma lipids were determined in male rabbits following 4 days of oral dosing with 0, 1, 10, or 100 mg/kg/day. In animals receiving 100 mg/kg, total cholesterol and triglycerides were increased approximately 3- and 10-fold, respectively, whereas HDL cholesterol was unchanged.

Changes in clinical biochemistry included increases in alkaline phosphatase (ALK), serum alanine aminotransferase (ALT), and serum aspartate aminotransferase (AST), sodium, and globulin and total bilirubin.

A study was conducted in rats to determine the neuropharmacological effects produced of up to 100 mg/kg/day bexarotene for four consecutive days. All rats exhibited normal social behaviour and body weight gain. There were no changes in body temperature.

Pharmacokinetics

Single-dose studies

Oral administration

Plasma bexarotene concentration data from pharmacokinetic and toxicity studies in the rat and dog demonstrated that bexarotene was orally bioavailable. The increase in plasma AUC values appeared proportional at lower doses and less than dose-proportional at higher doses. From oil formulations, nonmicronised bexarotene was 30-40% bioavailable in rats and 7.5% bioavailable in dogs. Maximum plasma bexarotene concentrations (C_{max}) generally occurred a few hours post-dose (t_{max} =2 to 4 hr).

Intravenous (i.v.) administration

Following i.v. administration of bexarotene, clearance was 10 to 20 ml/min/kg in the rat and 2 to 4 ml/min/kg in the dog. I.v. kinetics in plasma appeared multiphasic in both species. The $t_{½}$ of

bexarotene was 2 hr to 3 hr in rats and 3 hr to 6 hr in dogs. Bexarotene's volume of distribution was close to 1 l/kg, consistent with minimal retention of bexarotene in the extravascular tissues. There was no overall sex difference in pharmacokinetics in either species.

Repeat dose studies

In rats repeat dose C_{max} and AUC values increased with increasing dose but were less than dose proportional. Plasma bexarotene concentrations in rats were almost always dose-dependently lower after repeat-dose administration than concentrations after a single dose. The extent of this reduction in concentrations generally did not increase beyond 28 days of dosing. The magnitude of the reduction tended to be greater in male rats than in female rats.

In all of the toxicity studies conducted in dogs, systemic exposure to bexarotene was dose-dependent. There was dose-dependent reduction in exposure associated with repeated dosing. In a 28-day toxicity study in which nonmicronised bexarotene was administered in babassu oil at 10 to 200 mg/kg/day, C_{max} and $AUC_{(0-6)}$ values were 2-fold and 4-fold lower respectively on day 28 compared to day 1 at 10 mg/kg and 3-fold and 6-fold lower at 30 mg/kg.

Absorption

The oral bioavailability of bexarotene was formulation-dependent. For micronised drug in rat and nonmicronised drug in dog, suspensions in oil tended to provide greater bioavailability than suspensions containing PEG. Bioavailability of nonmicronised bexarotene was also significantly greater from a PEG-based solution formulation than that from oil- or PEG-based suspension formulations in dogs. These data suggested that dissolution may be rate-limiting for drug absorption and that bexarotene particle size reduction could enhance bioavailability. These studies established that micronised bexarotene was about six times more bioavailable than nonmicronised bexarotene and that different lots of micronised bexarotene exhibited similar pharmacokinetics. An experimental lot of clinical capsules that developed pellicles in dissolution testing displayed pharmacokinetics similar to one that did not form pellicles. The Marketing Authorisation Holder stated that data from these studies aided in selection of the clinical dose in transitioning from nonmicronised to micronised bexarotene in phase I-II trials, and setting bexarotene particle size specifications for Targretin capsules intended for commercial use.

Distribution

A study in rats demonstrated that drug-related radioactivity distributed essentially throughout the body after an oral dose of radiolabelled bexarotene. At the 4-hr time point, radioactivity was present in all of the 26 tissues examined. Other than organs of the gastro-intestinal tract, tissue-to-plasma radioactivity ratios were greatest in liver, kidneys and adrenals over four timepoints examined (4, 8, 24 and 48 hrs). No substantial retention occurred in any tissue; less than 1% of the radioactivity remained in the rats at 48 hrs.

A study in athymic mice revealed that bexarotene was capable of penetrating into solid tumour.

Protein binding studies

Bexarotene was highly protein bound (>99.9%) at concentrations present in the rat and dog plasma in toxicity studies.

Metabolism

In the rat and dog bexarotene was metabolised primarily by P450-dependent oxidation and glucuronidation. Systemic exposure to these metabolites (6- or 7-hydroxy-bexarotene and 6- or 7- oxo-bexarotene) was found to be less than that to parent compound after both single and multiple doses. 6-Hydroxy-bexarotene was a major circulating metabolite of bexarotene and glucuronides were the most prevalent bexarotene metabolites in bile. In rats, the primary biliary glucuronide was the acyl glucuronide of the parent compound. In dogs, the primary biliary glucuronide was the acyl glucuronide of 6- or 7-hydroxy-bexarotene. Overall bexarotene metabolism was qualitatively similar between the rat and the dog.

Excretion

In a rat oral-dose tissue distribution study using 100 mg/kg radiolabelled bexarotene, >90% of the radioactivity was excreted in the faeces by 48 hours in both sexes. Presence of the majority of excreted bexarotene in the faeces after an i.v. dose provided evidence for hepatobiliary excretion of the compound. The metabolism and excretion data indicated that the hepatobiliary excretion and subsequent faecal elimination of glucuronide conjugates (or parent compound in the dog) constitute the primary and almost exclusive means of bexarotene elimination in the rat and dog.

Enzyme induction

A rat study revealed that 4 days of daily, oral bexarotene treatment (600 mg/m^2) significantly increased (by 91%) gross hepatic microsomal cytochrome P450. Levels of some specific cytochrome P450 isozymes decreased significantly (90% for CYP1A2 and 41% for CYP2C11) while others increased significantly (CYP2B1/B2 by 28-fold, CYP3A by 8.2-fold and CYP4A by 71-fold). Rates of cytochrome P450 and glucuronyltransferase-mediated bexarotene metabolism were increased significantly in these microsomal preparations (by 252% and 77%, respectively), further supporting metabolic induction by bexarotene as a potential mechanism contributing to the reduction of systemic exposure after repeated dosing.

Other studies

Pharmacokinetic data were collected during two repeated dose pharmacodynamic studies of bexarotene in rats. Systemic drug exposure was dose-dependent and lower than dose-proportional in both studies.

Transferability across the placenta and distribution into milk

Studies in animals have shown reproductive toxicity. Based on the comparison of animal and patient exposures to bexarotene, a margin of safety for human teratogenicity has not been demonstrated. Bexarotene is contraindicated in pregnancy.
It is not known whether bexarotene is excreted in human milk. Bexarotene should not be used in breast-feeding mothers. This information has been included in the SPC (See section 4.6 *Pregnancy and lactation)*.

Systemic exposure in animals compared to patients

C_{max} and AUC increase proportionally to the dose in dog and in rat at the lower doses, and less than proportionally at higher doses. Plasma concentrations depend on dose, formulation and duration of treatment. Consequently, the exposure must be estimated by measured concentrations (AUC)

Table 1: Systemic exposure in preclinical and clinical studies

Species	**Rat n = 10/sex**		**Dog n = 6/sex/Dose**		**Patients**
Formulation			Capsule		Capsule
Dose	3 mg/kg		1 mg/kg (NOEL)	3 mg/kg	300 mg/m²
AUC h.µM	D178		W26	W26	Daily
	M	F	M+F	M+F	M+F
	4.7	8.1	4.2	9.8	11

There does not appear to be a safety margin relative to human clinical exposure.

Toxicology

Single dose toxicity

In the rat the maximum feasible single dose of 1500 mg/kg nonmicronised bexarotene suspended in sesame oil induced no treatment-related toxicity.

Administration to 2 dogs/sex/group at 0 or 720 mg/kg (maximum feasible dose in this species) elicited transient decreases in body weight and in serum cholesterol, LDL and HDL. There were no treatment-related findings at gross pathology. Pharmacokinetic analyses at fixed intervals post-dose revealed mean bexarotene C_{max} and AUC values of up to 60,800 ng/ml and 565,000 ng.h/ml respectively. On a AUC basis the systemic exposure was 112 (males) to 148 (females) times higher than that in patients at the recommended initial human dose (AUC of 3797 ng.h/ml after 300 mg/m^2/day multiple dose).

Repeated dose toxicity

Repeat dose toxicity studies (according to GLP) consisted of oral dose studies of approximately 4 week, 3 months and 6 months duration in the rat and dog (with 28 day recovery periods).
The main adverse treatment related findings were:

- Mortality related to serious coagulopathy in rats
- Hepatic toxicity in rats and dogs
- Cataracts in rats and dogs
- Adrenal gland hypertrophy in rats and dogs
- Testicular degeneration in dogs.

Other adverse treatment related findings were:

- Adverse local tolerance effects in the rat
- Effects on haematology parameters in rats and dogs
- Effects on haematopoietic tissues in the dog

Mortality related to serious coagulopathy in rats

In the repeat-dose rat studies, dose-related mortality due to haemorrhage and serious coagulopathy was associated with bexarotene administered at doses $\geq$ 10 mg/kg/day in sesame oil suspension by gavage or in a diet. The coagulopathy was associated with bexarotene-related prolongation of prothrombin (PT) and Activated Partial Thromboplastin Time (APTT) (>30 seconds). Vitamin K supplementation reduced the coagulopathy.
In 3-month and 6-month studies in rats in which bexarotene was administered by gavage in a PEG/aqueous suspension, haemorrhage due to serious coagulopathy was not observed, despite findings of higher PT and APTT in male rats compared to controls. PT or APTT was not increased in females. Deaths in these studies appeared to be related to gavage injury as the major precipitating event possibly related to hyperkeratosis induced in the oesaphagus (see below).
In contrast to the rat, no deaths related to serious coagulopathy occurred in the dog studies. Therefore this finding appears to be related to the oral administration of sesame oil to rats.

Liver toxicity in rats and dogs

Reversible hepatomegaly occurred in rats and dogs following repeat dosing with bexarotene. In both species, the liver returned to a normal size by the end of a 28-day treatment-free recovery period.
The increase in liver weight was associated with increases in the serum levels of the liver enzymes. In addition hepatocellular degeneration, necrosis, vacuolisation and pigment deposition were present. The effects were reversible following the 28-day treatment-free recovery periods. In the 6-month rat study with a 3-month interim sacrifice up to a 100% increase in liver weight associated with liver hypertrophy was observed at 2 to 3 months. There was no liver hypertrophy at 6 months of treatment, suggesting an adaptation to the drug effects.
In the 3-month dog study, no liver weight increases or adverse liver histopathology were observed after 91 days of treatment with nonmicronised bexarotene doses up to 1.5 mg/kg/day. By contrast in the 6-month dog study there were significant increases in relative liver weights associated with liver hypertrophy at 3 or 10 mg/kg/day micronised bexarotene. After a 4-week recovery period, relative liver weights of treated dogs were comparable to controls; however, slight liver hypertrophy was still present in all dogs at the end of recovery. No liver effects occurred at 1 mg/kg/day.
In conclusion, the adverse treatment related effects on the liver observed in two species appeared to be mainly almost completely reversible upon cessation of treatment.

Cataracts in rats and dogs

In the 6-month studies in rats and dogs dose-related posterior subcapsular cataracts developed in both species.

Cataracts in the rats were more severe and progressive than in dogs. In the 6-month rat study, prior to early sacrifice in week 8 of the 300 mg/kg/day (top) dose group there was a 51% incidence of cataracts. The cataracts increased in severity and incidence during the course of treatment at 3, 30 and 100 mg/kg/day and were not reversible upon cessation of treatment. In dogs, cataracts affected only a limited area in the posterior capsule, were bilateral, and appeared non-progressive. In the 26-week study, cataract formation occurred after 11 weeks of treatment at 3 and 10 mg/kg/day and the incidence increased .at study termination.

The NOEL for cataracts in dogs was 1 mg/kg/day and in rats was <30 mg/kg/day. Based on AUC systemic exposure for doses inducing cataract formation, there does not appear to be a margin of safety relative to human clinical exposure. There was no evidence in either species that the cataracts were reversible upon cessation of treatment. The Marketing Authorisation Holder has not provided a mechanistic explanation for this finding, the aetiology of which is unexplained. Although this finding has not been reported in the clinical data, the seriousness and lack of reversibility make this finding a matter of concern..

Adrenal gland hypertrophy in rats and dogs

Dose-related transient increases in adrenal weights were a common finding, but were reversible upon treatment cessation. This finding is probably not of clinical relevance.

Testicular degeneration in dogs

Testicular tubular degeneration, reversible after treatment cessation, occurred only in sexually immature dogs ($\leq$ 5 months) that were treated for up to 3 months with $\geq$ 0.1 mg/kg/day of bexarotene. Sexually mature (>8 months) dogs given daily doses of bexarotene for 6 months did not show any testicular abnormalities even at higher doses (up to 10 mg/kg). This finding is probably not of clinical relevance.

Adverse local tolerance effects in the rat

Acanthosis and hyperkeratosis of the epithelium in the non-glandular stomach and acanthosis of the skin occurred at $\geq$ 30 mg/kg/day in the rat 6-month study. This finding was reversible upon cessation of treatment.

Effects on haematology parameters in rats and dogs

In the rat 6-month and the dog 26-week studies the haematocrit, haemoglobin and erythrocyte values were decreased and the platelet count increased. These findings were reversible.

Effects on haematological tissue in the dog

Hypercellularity of haematopoietic cells in sternal bone marrow occurred in 5/12 dogs at the top dose of 10 mg/kg/day. The study report did not state whether this finding was reversible. It does not seem to have occurred in other studies.

Genotoxicity

Bexarotene was not genotoxic in the standard genotoxicity test battery in vitro and in vivo.

Carcinogenicity

In view of the proposed therapeutic indication and intended patient population, carcinogenicity studies are not considered necessary.

Reproduction toxicity

Fertility studies have not been carried out. A possible impact on fertility can not be excluded.

A dose range finding (conducted at up to 65 mg/kg/day p.o.) and a definitive study (at up to 16 mg/kg/day p.o.) were conducted to evaluate the potential for developmental toxicity of bexarotene in

rats. These studies demonstrated that bexarotene, in common with the majority of retinoids, was both teratogenic and embryotoxic in oral-dose studies at systemic exposures achieved clinically in patients.
The teratogenic effects of retinoids are well documented therefore it was not considered necessary to conduct further studies.
Bexarotene is contraindicated both in pregnancy and during lactation. Advice is given that women of childbearing potential should employ adequate birth control measures (see section 4.6 *Pregnancy and lactation*).

Local tolerance

In support of the parallel clinical development of bexarotene gel as a topical product, the local tolerance of bexarotene was investigated.
Dermal toxicity assessed in a 28 day study in the rat at gel strengths of 0.01%, 0.1% or 1.0% w/w revealed time and dose-related increased incidence and severity of erythema (slight to mild), epidermal scaling, scabbing and thickening, confined to the site of administration.
Bexarotene topical gel at $\leq$ 1.0% w/w did not appear to be a skin sensitiser in the guinea pig. Treatment related reactions appeared to be dermal irritation, possibly associated with some component of the vehicle, based on the similarity of reaction in vehicle and test article formulations.

Ecotoxicity/Environmental risk assessment

The Marketing Authorisation Holder states that bexarotene will not be manufactured in the E.U. The expected patient numbers in the E.U. is not anticipated to exceed 1200 patients/annum, therefore it is a low volume compound. Its therapeutic use is not considered to have an immediate effect on the environment.

Other toxicity studies

High concentrations of bexarotene appear to have a weak potential to be phototoxic and photo-irritating as determined by *in vitro* haemoglobin oxidation and histidine assays respectively. Bexarotene was not photocytotoxic in a human skin model of normal epidermal keratinocytes. A protein photo-binding assay in human serum albumin showed that bexarotene is capable of photo-induced binding and therefore may be a potential photoallergen.

Discussion on toxico-pharmacological aspects

Bexarotene is a new synthetic retinoid that binds selectively to three RXR receptors. The link between bexarotene-mediated RXR signalling and the effect in CTCL has not been precisely established. The retinoids, including RXR-selective ligands, can modulate T-cell biology, which can have relevance for a possible mechanism of action of bexarotene in CTCL.
Bexarotene formulations used in preclinical studies have changed during development. Suspensions of nonmicronised bexarotene in sesame oil (rats) and babassu oil (dogs) were used in preliminary studies. These suspensions were replaced by suspensions in polyethylene glycol 400 (PEG) and nonmicronised bexarotene was replaced with micronised bexarotene, used in the pivotal 26-week dog and rat studies.
Bexarotene was bioavailable following oral administration in both test species. Systemic exposure was decreased upon repeat dosing, which could be attributed to metabolic enzyme induction.
Interaction studies were not performed, as reflected in the SPC. These studies will be performed as a post-marketing commitment.
In repeated dose-toxicity studies conducted in rats and in dogs, the target organs of bexarotene were eyes (cataractogenic in both rats and dogs with no signs of recovery after 28 days), liver (weight increase, hypertrophy, biliary stasis in dogs, glycogen deposition in rats, slight necrosis in both species), adrenals (weight increase, some vacuolisation of cortical cells) and haematological parameters (reduction in RBC count, increase in platelet count, prolongation of PT and APTT in rats). In rats, bexarotene induced hyperkeratosis and acanthosis of the oesophagus and the non-glandular stomach and follicular atrophy and acanthosis of the skin.
Mortality was observed in both species. Hyperkeratosis of the oesophagus was probably the cause of gavage-related injury leading to an increase of the mortality in treated rats; however, the cause of death was not clearly established in treated dogs.
Bexarotene was cataractogenic at dosages comparable to human exposition. The Marketing Authorisation Holder partially addressed the mechanism of cataract formation in animal studies.

However, the relevance of animal findings to the human situation is still not clear. Moreover, the clinical follow-up of patients was not long enough to exclude a cataractogenic effect of bexarotene treatment. The Marketing Authorisation Holder will closely monitor this effect.
Bexarotene is teratogenic and embryotoxic at dosages comparable to human exposure. Fertility and peri- and post-natal effects of bexarotene were not evaluated. The use of bexarotene has to be contraindicated during pregnancy. Adequate birth-control measures have to be employed by women of childbearing potential.

Bexarotene is not mutagenic. Carcinogenicity studies have not been performed.

4. Clinical aspects

Introduction
The clinical trials were performed according to GCP standards and agreed ethical principles.

Clinical pharmacology
A total of three dose-ranging phase I-II involving 141 cancer patients were conducted. See Table 2.

Table 2: Dose-ranging studies

Protocol no.	Design/Phase	N	Tumour	Duration of treatment	Treatment
L1069-93-01	Phase I, open, dose-escalation	52	Advanced cancer	≥4 weeks	QD : 5, 20 and 40 mg/m^2/day of non-micronised bexarotene, 18, 50, 140, 300 and 400 mg/m^2/day of micronised bexarotene
L1069-93-02	Phase I-IIa, open, dose-escalation	60	Advanced cancer	4 weeks	QD non-micronised bexarotene: 5, 10, 20, 30, 45, 75 mg/m^2/day micronised bexarotene : 5, 10, 20, 30, 45, 75, 21, 50, 83, 140, 230, 380, 500, 650, 800, 1000 mg/m^2/day
L1069-94-02	Phase I-II, open, dose-escalation	29	Advanced head and neck squamous cell cancer	≥4 weeks	QD : 10 mg/m^2/day of non-micronised bexarotene ; BID : 25, 50, 150, 200, 300 mg/m^2/day of micronised bexarotene

There were a further 11 studies where Targretin capsules were given to approximately 500 patients with a range of diagnoses from advanced solid tumours, psoriasis and diabetes mellitus. In these studies the doses ranged from 5-1000 mg/m^2/day.

Pharmacodynamics

Mechanism of action
Bexarotene is a synthetic compound that exerts its biological action through selective binding and activation of the three retinoid X receptors (RXRs): RXRα, β, and γ. Once activated, these receptors function as transcription factors that regulate processes such as cellular differentiation and proliferation, apoptosis, and insulin sensitisation. The ability of the RXRs to form heterodimers with various receptor partners that are important in cellular function and in physiology indicates that the biological activities of bexarotene are more diverse than those of compounds that activate the retinoic acid receptors (RARs).
It is not known if the clinical response is supported only by the RXR activation effect.

Pharmacokinetic data (plasma levels obtained after Targretin administration) and *in vitro* binding data suggested that a continuous activation of RXR receptors is obtained after the administration of the initial dose of 300 mg/m²/day. Additionally a partial activation of RAR receptors may also be obtained.
The plasma concentrations of Targretin observed after repeated dose administration suggested that activation of RXR receptors could be obtained at peak as well as at trough concentrations.
RAR activation is unlikely to be obtained at trough concentrations.

Dose finding studies

At least three patients at each dose level were evaluated. If, after two weeks of treatment, no dose-limiting toxicity (DLT) was observed in the first three patients, then three patients could be entered into the next higher dose level. The MTD was defined as the highest dose level that resulted in no more than one patient experiencing a DLT among at least six patients who had completed at least four weeks of treatment.
The studies began with the non-micronised formulation of bexarotene. Because of a change in formulation, the micronised formulation of bexarotene was introduced at one-sixth the daily dose of the original non-micronised formulation. The micronised formulation of bexarotene was considered to have 6 to 8 times better oral bioavailability than the non-micronised formulation.
There were 9 patients with CTCL enrolled in L1069-93-01 study. Two of 9 patients improved while on bexarotene, which provided an early indication of bexarotene in CTCL. These patients responded to low doses of Targretin capsules (5 mg/m^2/day and 20 mg/m^2/day of non-micronised formulation). Four other CTCL patients treated in the range of 10 to 65 mg/m^2/day of non-micronised formulation and three patients treated in the range of 230 to 300 mg/m^2/day of the micronised formulation did not respond.
The recommendation regarding BID or QD dosing could not be made based on small number of patients studied at each dosing schedule in L1069-94-02 study.
The initial starting dose chosen was the MTD determined from study L1069-93-02 (650 mg/m^2/day). The low dose level in one treatment arm in L1069-23 study (6,5 mg/m^2/day) was selected to approximate the dose level (adjusted for the micronised formulation) at which responses were observed in L1069-93-01 study.

Pharmacokinetics

Introduction

The pharmacokinetics of bexarotene were evaluated during 6 clinical studies in patients with advanced cancers (3 studies), type II diabetes mellitus (1 study) and CTCL (2 studies). One study of relative bioavailability of Targretin capsules 75 mg and a bexarotene suspension has also been performed in 12 healthy volunteers:
Most patients were males (2/3), with the median age of 60 years. Tested treatments were administered concomitantly with food intake after 8-hour diet. The patients were not to have received other drugs susceptible to alter renal or hepatic function. Pharmacokinetics were linear up to a dose of 650 mg/m^2.

Absorption

Initial data from patients in trial L1069-93-01 and L1069-93-02 showed that the micronised formulation had significantly greater bioavailability than the non-micronised form (n=10) and only the micronised form was used for the rest of the trial. The initial half-life was 1.4 h with no accumulation with multiple daily doses.
Over the dose range proposed in the SPC, the half-life was approximately 2 h and the C_{max} and AUC increased dose proportionally. Absorption was enhanced by about 40% when bexarotene was taken with a fat containing dietary supplement in diabetic patients.
Bioavailability (C_{max} and AUC) decrease of Targretin after repeated administration is observed only in animal models during preclinical studies and in patients with no CTCL, enrolled in phase I and phase II studies. This decrease of Targretin bioavailability was explained by the existence of an auto-induction of Targretin metabolism.
These findings suggested that auto-induction might alter bioavailability of Targretin in patients with CTCL and consequently its clinical effect after repeated dosing. Nevertheless, PK studies conducted in

patients with CTCL at the recommended doses, shows no alteration of the bioavailability of Targretin in this patient group, suggesting that metabolic capacity of patients with CTCL is not altered after reiterated dosing.
Additionally, clinical experience shows that therapeutic response to bexarotene continued to occur at least up to 26,6 weeks after the initiation of the treatment.

A decrease of plasma concentrations depending of the duration of treatment was observed in preclinical studies in rat and dog. These observations were consistent with an auto-induction of bexarotene metabolism.
In humans, there was no decrease of plasma concentrations after multiple dosing in patients with CTCL. During phase I-II studies a reduction of bexarotene concentrations was observed within 15 days of dosing. For these patients no further decrease of plasma concentrations was observed after day 15.
The mechanism causing the lowering of plasma levels after multiple dosing was investigated in animal models (rat hepatic microsomes). An increase cytochrome P450 iso-enzyme was specifically observed with CYP3A4 after repeated administration of bexarotene.
In conclusion, a potential of auto-induction of metabolism of Targretin exists. But, no consequences of this mechanism have been observed in patients with CTCL at the recommended doses.

Protein binding

In study RR-845-99-002 the binding of radiolabelled drug to plasma proteins was high at 99.8-99.9% and was independent of the bexarotene concentration over the range tested.

Metabolism

The predominant plasma metabolites are formed by oxidation at the C-6 and C-7 positions to form 6- and 7-hydroxy-bexarotene and bexarotene acyl glucuronide. For all metabolites the C-6 isomer predominated over C-7 in humans. *In vitro* studies suggest that cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for formation of the oxidative metabolites. Based on the *in vitro* binding and the retinoid receptor activation profile of the metabolites, and on the relative amounts of individual metabolites in plasma, the metabolites have little impact on the pharmacological profile of retinoid receptor activation by bexarotene.

Elimination

There was no detectable difference in clearance with the first dose or multiple doses up to 400 mg/m^2/day in study L1069-93-01. The elimination half-life was approximately 1-3 hours when determined over a six-hour sampling interval. In some patients with 24-hour post sampling schedules the mean terminal elimination half-life was 7-9 hours.
Neither bexarotene nor its metabolites are excreted in urine in any appreciable amounts. The estimated renal clearance of bexarotene is less than 1 ml/minute. Faecal excretion was not measured, but it is assumed that elimination of the drug and its metabolites are primarily hepatobiliary.

Pharmacokinetics in special populations

No formal studies to assess kinetics in special patient populations have been performed
Use in children and adolescents: Targretin should not be used in a paediatric population until further data become available.
Use in the elderly: of the total number of patients with CTCL in clinical studies, 61% were 60 years or older, while 30% were 70 years or older. No overall differences in safety were observed between patients 70 years or older and younger patients, but greater sensitivity of some older individuals to Targretin capsules cannot be ruled out. The standard dose should be used in the elderly.
Renal insufficiency: no formal studies have been conducted in patients with renal insufficiency. Clinical pharmacokinetic data indicate that urinary elimination of bexarotene and its metabolites is a minor excretory pathway for bexarotene. In all evaluated patients, the estimated renal clearance of bexarotene was less than 1 ml/minute. In view of the limited data, patients with renal insufficiency should be monitored carefully while on Targretin capsule therapy.
Hepatic insufficiency: no formal studies have been conducted in patients with hepatic insufficiency. Clinical and animal pharmacokinetic data suggest that bexarotene is eliminated through hepatobiliary

mechanisms. Although there was no evidence for altered bexarotene pharmacokinetics in patients with elevated serum bilirubin, SGPT/ALT, SGOT/AST, or alkaline phosphatase, patients with hepatic insufficiency may theoretically have altered bexarotene pharmacokinetics. Therefore, patients with hepatic insufficiency should be monitored carefully while on Targretin capsule therapy.
Sex and ethnic origin: No relationship in the kinetics between sex or ethnic origin was studied.

Interaction studies
The data are limited. Therefore the Marketing Authorisation Holder has agreed to perform further interaction studies (see section II.3, *Follow-up measures of the Marketing Authorisation Holder*).
Drug interactions: effects of other substances on bexarotene: No formal studies to evaluate drug interactions with bexarotene have been conducted. On the basis of the oxidative metabolism of bexarotene by cytochrome P450 3A4 (CYP3A4), co-administration with other CYP substrates such as ketoconazole, itraconazole, protease inhibitors, clarithromycin and erythromycin may theoretically lead to an increase in plasma bexarotene concentrations. Furthermore, co-administration with CYP3A4 inducers, such as rifampicin, phenytoin, dexamethasone, or phenobarbital may theoretically cause a reduction in plasma bexarotene concentrations.
A population analysis of plasma bexarotene concentrations in patients with CTCL indicated that concomitant administration of gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene. The mechanism of this interaction is unknown.
There are some retrospective data on kinetics from study L1069-23 for patients taking levothyroxine, atorvastatin and gemfibrozil. Bexarotene concentrations were not affected by concomitant administration of atorvastatin or levothyroxine. Concomitant administration of gemfibrozil with Targretin capsules is not recommended.
Drug interactions: effects of bexarotene on other substances: There are indication that bexarotene may induce CYP3A4. Therefore, repeated administration of bexarotene may result in an auto-induction of its own metabolism and, particularly at dose levels greater than 300 mg/m^2/day, may increase the rate of metabolism and reduce plasma concentrations of other substances metabolised by cytochrome P450 3A4. For example bexarotene may reduce the efficacy of oral contraceptives.

After the granting of the Authorisation of Targretin, the MAH submitted a variation application on the basis of the interim analysis report of clinical trial L1069-34. This is an open-label, multicenter Phase II study for the "Evaluation of Targretin (bexarotene) capsules in Patients with Advanced Breast Cancer" to determine the activity of Targretin at two different dose levels in the treatment of women with metastatic breast cancer. Secondary objectives included determination of bexarotene pharmacokinetics in women with breast cancer and determination of plasma tamoxifen concentrations in women receiving concomitant Targretin capsules and tamoxifen therapy. The mechanism of the observed interaction between bexarotene and tamoxifen is unclear and the clinical significance of the diminution of tamoxifen AUC (35%) is not established. The CPMP considered that the most appropriate way to include this information on a possible interaction would be to modify the statement under section 4.5 of the Summary of Product Characteristics:
*"Bexarotene may increase the rate of metabolism and reduce plasma concentrations of other substances metabolised by cytochrome P450 3A4**, such as tamoxifen**."*

Laboratory test interactions: CA125 assay values in patients with ovarian cancer may be accentuated with Targretin capsule therapy.

Food interactions: in all clinical trials, patients were instructed to take Targretin capsules with or immediately following a meal. In one clinical study, plasma bexarotene AUC and C_{max} values were substantially higher following the administration of a fat-containing meal versus those following the administration of a glucose solution. Because safety and efficacy data from clinical trials are based upon administration with food, it is recommended that Targretin capsules be administered with food.

On the basis of the oxidative metabolism of bexarotene by cytochrome P450 3A4, grapefruit juice may theoretically lead to an increase in plasma bexarotene concentrations.

Bioequivalence studies

One study of relative bioavailability of Targretin capsules 75 mg and a bexarotene suspension has been performed in 12 healthy volunteers. As usual after an oral administration of a retinoid great interpatient variations were observed both in C_{max} and AUC levels. The results were as follows:

Table 3: Bioavailability of capsule relative to suspension. This was a randomised, open, 2-period, cross over study in 12 healthy volunteers. Dose was 75 mg.

	t_{max} h	**C_{max} ng/ml**	**AUC 0-7 h.ng/ml**	**AUC 0-∞ h.ng/ml**	**$t_{½}$ h**
Suspension (reference)	1.5	99	355	368	1.9
Capsule	2.8	77	313	332	2.2
90 % confidence interval	-	60-106 %	-	75-127 %	-

Clinical Efficacy

A total of 16 clinical studies were performed:

- 2 pivotal phase II-III studies in patients with CTCL
- 14 uncontrolled open studies in patients with non-CTCL cancers or benign diseases. 3 dose-ranging studies have already been discussed in the clinical pharmacology section and are not included in the table below.

Table 4: overview of clinical studies

Protocol number	**Designs, blinding assignment, indication**	**N**	**Intended duration**	**Initially assigned dose range in mg/m²/day (Formulation) Dose frequency**	**Range of duration of treatment (days)**
PIVOTAL STUDIES					
L-1069-23	Phase II-III, open-label, untreated refractory CTCL	86	16 weeks with option to continue	6,5 650	N/A
L-1069-24	Phase II-III, open-label, untreated refractory CTCL	107	16 weeks with option to continue	650	N/A
MONOTHERAPY NON-CTCL ONCOLOGY STUDIES					
L1069-20	Phase II-III, double-blind, placebo-controlled, non-small cell lung cancer		4 weeks with option to continue	300-600 QD	1-431
L1069-21	Phase II, open-label, Kaposi's sarcoma		16 weeks with option to continue	650 QD	1-548
L1069-22	Phase II, open-label, prostate cancer		4 weeks with option to continue	300–600 QD	1-165
L1069-26	Phase II, open-label, asymptomatic ovarian cancer		12 weeks	600 QD	20-85

L1069-28	Phase II dose escalation, feasibility, open-label, pre-surgery head and neck cancer		7 days	200 QD	7-9
L1069-32	Phase II, open-label, malignant melanoma		8 weeks with option to continue	450 QD	27-130
L1069-33	Phase II, open-label, liposarcoma		8 weeks with option to continue	150 QD	1-126
COMBINATION THERAPY NON-CTCL ONCOLOGY STUDIES					
L1069-17	Phase II combination therapy with INTRON® A, open-label, advanced renal cell carcinoma		16 weeks	200-600 QD	1-484
L1069-18	Phase I-II dose escalation in combination with vinorelbine and cisplatin, open-label, advanced non-small-cell lung cancer		4 weeks	150-600 QD	7-239
OTHER NON-CTCL STUDIES					
L1069-29	Phase II, open-label, dose ranging, plaque psoriasis.		12 weeks	1-2 mg/kg/day QD	5-131
L1069-DM-01	Phase II open-label, monotherapy, non-insulin dependent diabetes		12 weeks.	20 mg BID 75-300 mg/day QD	22-43 2-273

NM = non-micronised

Dose-ranging efficacy studies were not performed. The dose regimen for phase II-III studies was determined with regard to the results of the 3 open-label, dose escalation studies (L1069-93-01, L1069-93-02 and L1069-94-02) in patients with various types of advanced cancers. See the pharmacodynamics section.

Main studies

The 2 pivotal phase II-III studies, L1069-23 and L1069-24, aimed to be historically controlled studies by a comparison to the natural evolution of patients with untreated refractory CTCL. The studies have followed International Conference on Harmonisation (ICH) for the ethical conduct of clinical trials.

The principal objectives of both studies were to evaluate the safety and antitumour efficacy of bexarotene in patients with refractory or persistent early stage CTCL and in patients with refractory advanced stage CTCL. Study L1069-23 aimed to evaluate two different daily doses of Targretin capsules in patients with refractory or persistent early stage CTCL, but was not powered to compare the two response rates.

General description

In L1069-23 study patients were to be randomised in a 1:1 ratio to low dose (6,5 mg/m^2/day) or to high dose (650 mg/m^2/day) bexarotene. In L1069-24 study all patients were initially treated by bexarotene 650 mg/m^2/day. Because of a high number of dose-limiting toxicities, the starting dose

level was successively reduced in both studies by protocol amendments from 650 mg/m^2/day to 500 mg/m^2/day and finally to 300 mg/m^2/day.

In addition, as patients on low dose bexarotene (6.5 mg/m^2/day) appeared to progress more frequently than those on the higher dose group, the study protocol L1069-23 was amended to stop the inclusions in the low dose group and to include all patients in 300 mg/m^2/day dose group. By the decision of the FDA, the randomisation between the two dose groups and the 6,5 mg/m^2/day dose group were re-introduced several months later.

The planned treatment duration was at least 16 weeks. The initial daily dose could have been decreased to 200 mg/m^2/day and than to 100 mg/m^2/day or temporarily interrupted (for less than 4 weeks) in case of toxicity. In case of no response after at least 8 weeks of therapy, the dose could have been increased to 400 mg/m^2/day or more if well tolerated. Patients with the initial dose of 6,5 mg/m^2/day could have their dose increased to 300 mg/m^2/day in case of no response after at least 8 weeks of therapy.

Inclusion and exclusion criteria

Patients were to have met the following:

- a clinical diagnosis of CTCL (stage I to IIA in L1069-23 study, stage IIB to IVB in L1069-24 study) confirmed by a biopsy within 30 days prior to entry
- refractory to, or intolerant to, or have reached a response plateau for at least 6 months on at least two prior therapies in study L1069-23 (PUVA, UVB, electron-beam therapy, photophereses, topical nitrogen mustard, BCNU, interferon, systemic cytotoxic chemotherapy). At least one of qualifying prior treatments must have been topical nitrogen mustard, BCNU or PUVA, UVB, or electron-beam therapy. Previous topical steroids and systemic retinoids did not qualify.
- refractory to at least one systemic cytotoxic chemotherapy in study L1069-24.
- Refractory CTCL**:** resistance to therapy due to lack of response of at least 50% improvement or progression on therapy after initial response.
- Intolerant CTCL: discontinuation of therapy due to side effects/toxicity, whether or not a response occurred.
- no antipruritic therapy or no change before and during the trial
- systemic therapy of CTCL indicated
- no topical CTCL treatment within 2 weeks, no PUVA or UVB within 3 weeks, no EBT, photopheresis, systemic anticancer therapy or oral retinoid therapy for any indication within 4 weeks prior to study entry.
- a Karnofsky performance score $\geq$60 and acceptable organ function (notably normal lipid levels)
- negative HCG test and effective means of contraception in female patients of child-bearing potential

The patients were followed up at week 2, week 4 and every 4 weeks during the treatment.

The patients were withdrawn from the study in case of disease progression, unacceptable toxicity or other medically important event. The use of topical corticosteroids as qualifying prior therapy meeting eligibility criteria was excluded in study L1069-23 for the purpose of assuring a more refractory population of patients for these studies. Topical steroids are commonly used in the very early stages of CTCL, often during the stages of disease prior to a diagnosis of CTCL. Because of the high frequency of use, especially in the earliest stages of CTCL, if topical steroids were allowed as a qualifying therapy the patient population would not have been as heavily treated or as refractory. Additionally, as a therapy often administered prior to a diagnosis of CTCL, there might have been some uncertainty about whether the topical steroid should be considered to have been administered for the treatment of CTCL or for some other, pre-CTCL diagnosed condition.

Efficacy evaluation

Primary efficacy endpoints were defined as the tumour response to treatment (clinical complete response [CCR] + partial response [PR]) determined by:

Physician's Global Assessment of Clinical Condition (PGA) and

Composite Assessment of Index Lesion Disease Severity (CA)

A patient was considered a responder if he met response criteria for either the PGA or the CA, which designated the Primary Endpoint Classification (PEC) for the study. The highest PEC between the PGA and CA for each patient was used for response calculation. It is accepted that the Primary Endpoint Classification (PEC) is not a standard approach to cancer therapy response rates. No attempt was made to blind Investigators performing clinical evaluations. However, the CA endpoint was based entirely on objective assessments of disease status. The CA endpoint was based on the five clinical signs of up to five index lesions representative of the patient's overall cutaneous disease. Precise serial measurements of all cutaneous lesions would not have been feasible. A total of 68% (103/152) of the patients enrolled had at least 20 (or considerably more) cutaneous CTCL lesions at baseline. The exact number of lesions was not recorded on the Case Report Form for these patients; precise and reliable tracking of multiple clinical signs for each of the lesions was considered unwieldy and impractical. The overall body surface area (BSA) involvement by CTCL is an independent and objective secondary efficacy endpoint. These data include all patients.

Physician's Global Assessment (PGA*)*

The Physician's Global Assessment (PGA) assessed the overall extent of improvement/worsening of the patient's overall disease compared to the condition at entry (at baseline), including both index and non-index cutaneous lesions, clinically abnormal lymph nodes, and all other CTCL disease manifestations, if present.

Table 5: Grading of Physician's Global Assessment (PGA) of Clinical Condition

Grade	Description	**Response**
0 Completely clear	No evidence of disease; 100% improvement	Clinical complete response (CCR)
1 Almost clear	Very significant clearance (≥90% to <100%); only traces of disease remains	Partial response (PR)
2 Marked improvement	Significant improvement (≥75% to <90%); some evidence of disease remains	
3 Moderate Improvement	Intermediate between slight and marked improvement; (≥50% to <75%)	
4 Slight Improvement	Some improvement (≥25% to <50%); however, significant evidence of disease remains	Stable disease (SD)
5 No change	Disease has not changed from baseline condition (± <25%)	
6 Worse	Disease is worse than at baseline evaluation by ≥25% or more	Progressive disease (PD)

In addition, Complete Response (CR) was defined by the PGA grade 0 and the absence of CTCL on cutaneous biopsy of a clinically cured lesion.

An improvement or worsening in the PGA grade must have been confirmed by two consecutive observations over at least four weeks. The response to Targretin capsule treatment was classified as CR, CCR, PR, SD, or PD (if PD preceded in time a better response the patient would be classified as PD)

Composite Assessment (CA) of Index Lesion Disease Severity

Up to five index lesions per patient were assessed and graded at each visit according on a 0-to-8 point scale (0=no lesion, 8=very severe lesion) with regard to scaling, erythema, plaque elevation, hypo/hyper-pigmentation, and surface area. For scaling, erythema, and hypo/hyperpigmenation intermediate intervals 1, 3, 5 and 7 were added to serve as mid-points between the defined grades 0, 2, 4, 6 and 8. The surface area in square centimetres (multiplication of 2 longest perpendicular diameters) was converted to a 0-to-18 scale (see Appendix) in order to be incorporated to CA grade.

Summing all the grades for each index lesion generated a CA grade. CA grade at baseline was then divided by CA grades at each subsequent visit to determine the CA ratio. CA ratio <1.0 indicated improvement in disease and a ratio >1.0 indicated a worsening of disease.

The definite CTCL response to treatment according to the CA endpoint was calculated by the

Marketing Authorisation Holder:

- Complete Response (CR): CA ratio=0, no skin lesions, no clinically abnormal lymph nodes or visceral tumours, and a cutaneous biopsy documenting absence of histology signs of CTCL from a cleared lesion
- Clinical Complete Response (CCR): CA ratio=0 and no skin lesions, no clinically abnormal lymph nodes or visceral tumours.
- Partial Response (PR): CA ratio≤0.5 and less than 25% increase in the number or aggregate area of clinically abnormal lymph nodes, cutaneous tumours or visceral disease and no new pathologically abnormal lymph nodes or new visceral disease in an area documented to be free of disease within 14 days of entry in the study
- Stable Disease (SD): If none of the previous response classifications accurately described the disease state, then the primary endpoint classification was SD.
- Progressive Disease (PD): CA ratio ≥1.25, and ≥25% increase in the number or aggregate area of clinically abnormal lymph nodes, cutaneous tumours, known pathologically abnormal lymph nodes or known visceral disease; or a new cutaneous tumour or new pathologically positive lymph node or new visceral disease in an area documented to be free of disease within 14 days of entry in the study

Confirmation by at least two assessments separated by at least four study weeks was required for a partial or complete response classification.

The Physician's Global Assessment (PGA) gives a global assessment of the improvement/worsening of the patient's overall disease compared to entry and can always be influenced by knowledge of the daily dose the patients received. The absence of placebo makes this primary endpoint extremely subjective. The composite Assessment (CA) of Index Lesion Disease Severity is a more objective measure of index lesion response to treatment. However, calculations of both CA grade and CA ratio were done by the Marketing Authorisation Holder. This signifies that the final response to treatment, according to the CA, was assessed by the Marketing Authorisation Holder and not by investigators.
The investigators graded index lesions' signs and symptoms, and assessed CTCL body surface area (BSA), lymph nodes and visceral involvement.
Neither total number of skin lesions nor new lesions were assessed. The information concerning these 2 points was approximately obtained by BSA of all lesions, (« patient's palm = 1% of BSA ») and notion « >20 lesions or <20 lesions ».

Secondary endpoints
The most important secondary end-points were:
- Time to response: a time interval from day 1 to the first confirmed response
- Duration of disease control: a time interval from first observation when the patient met response criteria (CR, CCR or PR) to the time that the patient relapsed. Durability of response: day of relapse (or last data point available for documenting continuation of response) minus day of onset of response, plus one day. A patient was considered to relapse if he first responded to treatment (CCR or PR) and then met the relapse criteria of a 25% or more worsening from the new baseline established at the time of response confirmation.
- Time to disease progression: a time interval from day 1 to PD
- The response (CCR+PR) to treatment of cutaneous disease (all lesions) determined as a percentage involvement of total body surface area (BSA): patient's palm = 1% of total BSA. BSA was determined for both patch and plaques lesions.

Supportive data
Index lesion photographs and drug concentration measurements at each visit.

Laboratory evaluations
Blood specimens were obtained at baseline and every 4 weeks for fasting triglycerides, fasting HDL, LDL and total cholesterol, liver function tests, thyroid hormones, serum amylase, creatine phosphokinase and blood coagulation parameters, complete blood count. The NCI common toxicity criteria were used to classify laboratory abnormalities.

Slit-lamp eye examination every 12 weeks was added by protocol amendment.

Statistical analysis

The expected objective response of untreated, refractory CTCL was considered 0%. Five percent was used as the theoretical maximum response rate. The success was defined by a CCR+PR ∃20% confirmed by at least 2 assessments separated by 4 weeks (significance level=0,05, historic control response rate=0,05 and alternative (Targretin) response rate=0,20). Sample size calculations provided that at least 30 patients would be required in each dose group to yield a 95% confidence interval for the true response rate of 5% to 35%. The study L1069-23 in patients with early stage CTCL was not powered to compare the two response rates by inferential statistics.

Study design of the study L1069-23 was changed twice: to one dose group with no randomisation and then again to two dose groups.

The definition of "refractory" was prospectively defined before the beginning of the trials. Patient enrolment commenced under Version 2 of the protocols, which included this definition. A patient who never responded to a given therapy might be characterised as "primarily" refractory to that therapy; a patient who initially responded and then progressed on a given therapy, might be characterised as "secondarily" refractory to that therapy.
For the total of 322 refractory prior therapies in both studies, 82% (264/322) were primarily refractory and only 18% (58/322) were secondarily refractory. A new, non-protocol-specified analysis included only patients primarily refractory to at least one systemic CTCL therapy. Patients secondarily refractory, intolerant, or having had a response plateau to prior therapy were not analysed.
These selection criteria were applied to 193 patients, included in both studies. These criteria produced a subset of 117 patients, including 24 patients from the early stage study and 93 patients from the advanced stage study.

Although the indication «refractory CTCL» represents a heterogeneous group of T-cell skin malignancies including classic Mycosis Fungoides and Sézary syndrome as the most common forms, this can be accepted.

In the recent period aggressive CTCL forms have become better individualised, and it might be possible nowadays to exclude these patients from enrolment because they need different, frequently more aggressive treatment. However, this distinction was probably impossible when the studies were realised.
In addition it might be impossible to enrol sufficient patients to power a study by individual sub-classification variants of CTCL. The incidence of CTCL in Europe has been estimated to be about 1,200 patients per year. The scarcity of clinical subjects has obvious practical implications for the clinical development programme.

Descriptions of techniques used

Point and interval estimation was the primary method for analysis. Summary statistics were provided for continuous variables. Frequency distribution and percent were presented for discrete variables.

For the purpose of analysis, patients have been grouped in three initial dose groups:
6.5 mg/m^2/day
300 mg/m^2/day
>300 mg/m^2/day

Study populations

In study L1069-23 the age of the patients ranged from 24-62 years, median 62, 82% were white and 64% male. The majority, 59%, had stage IB disease with only one patient with stage IIB who had 20 cutaneous tumours. The mean duration of the disease was over 13 years. Previous treatments included irradiation 97%, systemic therapy 59%, topical or local therapy 95%. The most common previous systemic therapy was interferon, 38%.

In study L1069-24 patients were 18 years or older with a clinical diagnosis of stage IIB-IVB CTCL confirmed by a lesion biopsy within 30 days of entry and no central nervous systems involvement. They were also to have been refractory to at least one systemic anticancer therapy for CTCL.

Efficacy results

Study L1069-23

Table 6: PGA and CA Response Rate

Response Classification	**PGA Dose (mg/m²/day)**			**CA of index lesions Dose (mg/m²/day)**		
	6. 5 N=15 (%)	**300 N=28 (%)**	**>300 N=15 (%)**	**6.5 N=15 (%)**	**300 N=28 (%)**	**>300 N=15 (%)**
CCR+PR	1(6.7)	14 (50)	9(60)	3 (20)	10 (36)	7 (46.7)
SD	6 (40)	10 (36)	5(33.3)	11(73.3)	13 (46.4)	6 (40)
PD	8 (53.3)	4 (14)	1 (6.7)	1 (6.7)	5 (17.6)	2 (13.3)

Study L1069-24

Ninety-four patients with advanced stage CTCL, refractory to at least one systemic therapy for CTCL were enrolled. For the purpose of analysis, patients were grouped in two dose groups:
300 mg/m²/day (N=56)
>300 mg/m²/day (N=38).
The study was not statistically powered to test for a difference in response rate between an initial dose of 300 mg/m²/day and >300 mg/m²/day.
The majority of patients included belonged to the stages IIB or III (skin involvement with tumours or erythroderma, no specific lymph node or visceral involvement).
96% (90/94) of all enrolled patients were considered refractory to at least one prior systemic therapy for CTCL. The median number of therapies for the 300 mg/m²/day initial dose group was 3 (range 0-6). One patient had no systemic therapy (protocol deviation).

Table 7: Most commonly used prior systemic anti-CTCL therapy

Prior therapies	**300 mg/m²/day**	**>300 mg/m²/day**
Interferon	59% (33/56)	74% (28/38)
Methotrexate	38% (21/56)	26% (10/38)
Combination chemotherapy	25% (14/56)	45% (17/38)
Corticosteroids	25% (14/56)	21% (8/38)
Photopheresis	21% (12/56)	32% (12/38)
Isotretinoin	8.9% (5/56)	34% (13/38)

Primary Efficacy Endpoints

Table 8: PGA and CA Response Rate

Response classification	**PGA Dose (mg/m²/day)**		**CA of index lesions Dose (mg/m²/day)**	
	300 N=56 (%)	**>300 N=38 (%)**	**300 N=56 (%)**	**>300 N=38 (%)**
CCR+PR CCR	27 (48.2) 0	20 (52.5) 2 (5)	15 (26.8) 1 (2)	18 (47.4) 5 (13)
SD	19 (34)	14 (37)	21 (37.5)	9 (23.7)
PD	10 (18)	4 (10.5)	20 (35.7)	11 (28.9)

Based on the 95% confidence intervals, the response rates were not statistically different for the 300 mg/m²/day and >300mg/m2/day groups for any parameter (PGA, CA, PEC). However, the study was not powered to test the difference between the two doses.

Most patients treated with >300 mg/m²/day had serial dose reductions or temporary interruptions of treatment.

Studies L1069-23 and L1069-24

Data on lymph nodes

Out of 152 patients, 84 patients were on 300 mg/m^2/day, 35% (29/84) had at least one clinically abnormal lymph node at baseline, 48% (14/29) responded, including 24% (7/29) of patients who had clinical complete resolution of all nodes present at baseline.

Data on cutaneous tumours

Out of 152 patients, 84 patients were on 300 mg/m^2/day, 19% (16/84) had at least one cutaneous tumour at baseline, 25% (4/16) of patients responded, including 6% (1/16) of patients who had clinical complete resolution out of all cutaneous tumours present at baseline.

Data on visceral involvement:

The clinical trial data regarding visceral involvement are too sparse to allow any conclusions about the possible efficacy of Targretin capsules regarding visceral disease.

Efficacy response

Response rates

Initially only the results for 152 patients were initially provided, as described above. Later on in the procedure the Marketing Authorisation Holder has analysed 193 patients included in both studies; 117 patients refractory to at least 1 systemic treatment were analysed, 24 early stage and 93 advanced stage CTCL patients. Of the 93 advanced stage patients refractory to at least one systemic treatment, 61 were treated at the recommended posology of a 300 mg/m²/day (32 patients were treated at doses higher than 300 mg/m²/day). The main characteristics of these patients are:

- Median age of 60 years
- 37.7% stage IIB, 31.1% stage III, 24.6% stage IVA and 6.6% stage IVB
- Median duration of CTCL of 8.9 years (range 0.7 to 31 years)
- overall BSA involvement by CTCL of 28%
- 74% of patients had at least 20 discrete cutaneous CTCL lesions
- 56% had at least one clinically abnormal lymph node at baseline; for those patients, the median number of nodes was three (range 1 to 13)
- 31% had at least one cutaneous tumour; for those patients, the median number of tumours was three (range one to 34)
- 23% of patients had at least one pathologically positive lymph node
- 3.3% (2 patients) had at least one site of visceral involvement
- Median number of prior systemic CTCL therapies was two (range one to six);
- The most frequent prior systemic therapy used was interferon, used by 59% of patients; the next most common systemic therapies were methotrexate (43%), combination chemotherapy (33%), and photopheresis (26%).
- The most common therapies to which the patients were refractory were interferon (52% of patients), methotrexate (33%), and photopheresis (20%)
- 66% of patients had been unresponsive (refractory) to all prior systemic CTCL therapies
- The median time on study was 19.9 weeks (range 2.0 to 117.7 weeks).
- The most common, the last/most recent, and the mean dose levels were 300 mg/m²/day
- The most common primary reasons for withdrawal were progressive disease (51% of patients), followed by adverse event (13%), administrative (11%), and partial response (8%)
- Dose modifications: there was no reduction of dose in 54% of patients; 39% of patients required temporary suspension of treatment.

The overall response rates (CCR + PR) were 31% (CA) and 51% (PGA). The clinical complete response rates were 6.6% by CA, 3.3% for PGA. The projected median time to progression was 16.1 weeks for CA. Responses were observed across all advanced stages of disease: stage IIB: 43% (10/23 patients), stage III: 16% (3/19 patients), stage IVA : 33% (5/15 patients) and stage IVB : 1/4 patients.

For the 30 patients in the SPC data set with at least one pre-existing clinically abnormal lymph node, 30% (9 patients) had at least 50% sustained improvement in the number of nodes and/or aggregate nodal area. Seven patients had at least transient complete resolution of all lymph nodes.

For the 14 patients in the SPC data set with at least one pre-existing cutaneous tumour, 21% (3 patients) had at least 50% sustained improvement in the number of tumours and/or aggregate volume of tumours. One patient had CCR, one patient had 97% reduction in aggregate tumour volume, and one patient experienced a 69% reduction in tumour volume.

Out of 24 early stage CTCL patients refractory to at least one systemic therapy, 9 were treated with the recommended posology; the response rate for these patients was 67% (6/9 patients).

The responses were observed mostly in patients with stage IIB and IVA (cutaneous patches, plaques, and tumours, normal or abnormal lymph nodes and no visceral involvement). The most frequently given daily dose was 300 mg/m2/day; this dose should be adapted according to its safety profile in each patient.

Secondary end-points

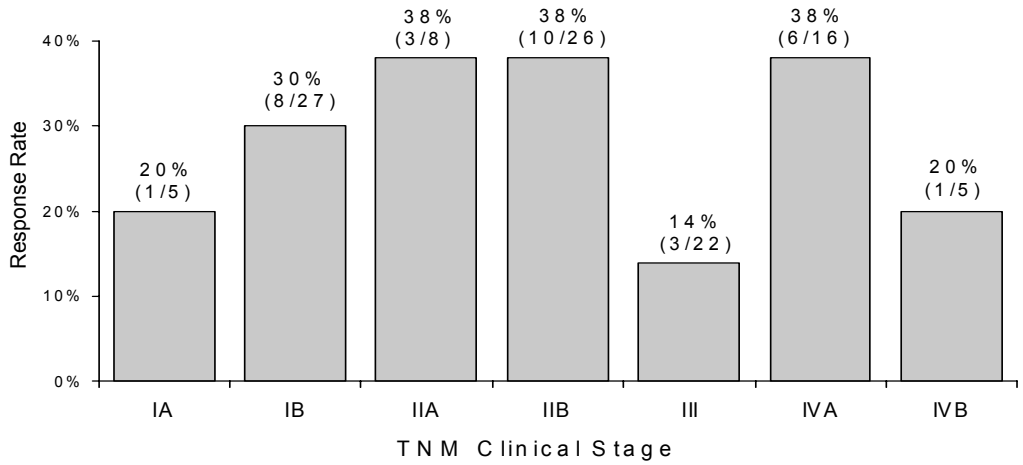
The secondary end-points time to relapse and time to progression of non-responders are difficult to interpret because of the relatively small number of patients per CTCL stage. Only the median BSA involvement (patch + plaque) by CTCL can be taken into account for the efficacy evaluation. Treatment with Targretin seems to decrease the BSA of CTCL skin lesions with approximately 10% (-9.5% to -16.3%). This response is evaluated in only 50% of patients treated.

Duration of treatment at recommended posology

Out of 193 patients treated, for 109 patients in the 300 mg/m^2/day dose group, the median duration of treatment was 19.7 weeks (range 0.4 to 84.6 weeks) and for 53 patients in the >300 mg/m^2/day dose it was 26.7 weeks (range 0.6 to 118 weeks).

Response rates by TNM stage of disease

Figure 1: Response rates for 300 mg/m^2/day, 32 responding patients/109 patients enrolled



Clinical studies in special populations

There were no formal studies in special patient populations. Retrospective data are available from studies in patients with advanced cancer or non-insulin dependent diabetes mellitus. No relationship in

the kinetics between age (adults compared to the elderly), sex or ethnic origin was studied. No studies have been performed in children.

Discussion on clinical efficacy

Choice of dose

The finally recommended dose (300 mg/m^2/day or 516 mg/day) was empirically decided, by decreasing the initial high dose due to toxicity. This dose still seems too high compared to other known retinoids. It should be noted that daily dose for isotretinoin should not exceed 1 mg/kg/day and for etretinate 75 mg/day. The average daily dose in the two studies was situated around 200 mg/m^2/day. Moreover, no clinical data exist on one versus two daily doses in CTCL patients.
However, the dose recommendation can be accepted, provided that this dose is adapted according to the safety profile in each individual patient to obtain the most acceptable benefit/risk ratio. This is reflected in the SPC (see section 4.2 *Posology and method of administration)*.

Efficacy results

No comparative study was provided. The two pivotal studies were open-label, phase II-III studies in patients with early stage CTCL, and in patients with advanced stage CTCL. Selected population comprised refractory, resistant or intolerant patients, or patients progressing after initial response to 1 or 2 previous treatments. Primary efficacy variable was tumour response to treatment, evaluated by one subjective endpoint (Physicians Global Assessment of clinical condition, PGA) and by one more objective endpoint (Composite Assessment of index lesion disease severity, CA). On the recommended posology (300 mg/m^2/day), the objective response rate was 36% in early stage CTCL patients, and 27% in advanced stage CTCL patients. Only the results for 152 patients were initially provided.

Later on in the procedure the Marketing Authorisation Holder has analysed 193 patients included in both studies; 117 patients refractory to at least 1 systemic treatment were analysed, 24 early stage and 93 advanced stage CTCL patients. The objective response rates in these patients (CA=34%) appears comparable to those observed in the initial submission.

Comparison of response rates

The Marketing Authorisation Holder has compared the response rates of advanced stage patients to response rates in the same patients at an earlier stage of the disease (within-patient controls) and to historical controls.

Historical controls

One older publication has been analysed (Bunn et al, Ann Intern Med, 1994;121:592-602). The response rates were the following (only monotherapy):
- interferon : CR+PR=55%, (CR=17%)
- other retinoids: CR+PR=58% (CR=19%)

Additional analysis of recently published literature revealed 11 monotherapy studies in patients with all clinical stages of CTCL and frequently not refractory to previous treatments:
- liposomal doxorubicin: CR+PR=83%, (CR=67%)
- interferon : CR+PR=62%, (CR=36%)
- trimetrexate: CR+PR=53%, (CR=6%)

Comparison to historical controls appears difficult because the patients treated by Targretin were refractory to at least one systemic treatment. Taking into account that the response rates in the literature were probably evaluated by the endpoints like PGA, it can be assumed that the efficacy of Targretin (300 mg/m²/day: CR+PR= 31% (CA) or 51% (PGA), CR=7%) is comparable to that of interferon and of other retinoids. However, the complete responses to Targretin are lower than those observed with other treatments.

Within-patient controls

The response to Targretin was compared to the best response to prior CTCL therapies in 93 advanced stage CTCL patients refractory to at least one systemic treatment. The responses to these prior therapies were assessed by the PGA endpoint (subjective investigator's judgement) in case report forms.

The most frequent previous systemic treatments were:

- single agent chemotherapy (different agents) (78 patients, CR+PR=14.1%), followed by
- interferon (59 patients, CR+PR=15.3%),
- combination chemotherapy (different regimens)(49 patients, CR+PR=36.7%) and
- other retinoids (29 patients, CR+PR=17.2%).

The overall response rate to Targretin was better than the response rates to all previous systemic therapies. The complete response to Targretin was lower than that obtained by other retinoids and combination chemotherapy.

The Marketing Authorisation Holder has provided data on the patients' response to prior topical and irradiation CTCL therapies (within-patient controls).

For prior topical therapies the overall response rates to Targretin exceeded the response rates to all prior topical therapies except topical retinoids (3 patients).

For prior irradiation therapies: overall response rates to Targretin (31%) were exceeded by the response rate for electron beam therapy (72%) and radiotherapy (38%). The response rate to Targretin was superior to those for photopheresis (30%) and PUVA (24%). The low response rates to topical therapy and PUVA therapy are understandable due to advanced stage and refractory character of the disease.

Clinical safety

Patient exposure

Safety data have been reported from 2 phase II-III clinical studies of 152 CTCL patients and from 9 open phase I-II, II and II-III clinical studies with 352 non-CTCL patients.

Safety data for 109 CTCL patients treated at the recommended posology have been analysed, based on a duration of exposure with a median of 19.7 weeks (range 3 days to 84.6 weeks).

A total of 47% (91/193) of all enrolled CTCL patients received at least 24 weeks of Targretin capsule therapy. These 91 patients were treated for a median of 308 days (mean 344 days, range 172 to 826 days). 49/91 patients were treated at the recommended posology. Comparison of the safety profile for these 49 patients to the safety profile for all patients at the recommended posology regardless of treatment duration shows that many events are modestly higher for patients treated more than 24 weeks.

The Four-Month Safety Update data, based on 810 patients treated with Targretin capsules entered into Ligand's database as of 30 July 1999, further confirm that Targretin capsules were generally acceptably tolerated.

Adverse events and serious adverse event/deaths

Adverse events by system and frequency are listed in Table 19.

Table 9: Summary of adverse events

Patients experiencing	152 CTCL patients	352 non-CTCL patients
Adverse event	98.7%	98.3%
Drug-related adverse event	98%	82.1%
Severe adverse event	27%	39.8%
Drug related severe adverse event	14.5%	18.2%
Serious adverse event	29.6%	29.8%
Drug-related serious adverse event	5.9%	3.1%
Withdrew due to adverse event	19.1%	10.8%
Withdrew due to drug-related adverse event	15.8%	8.2%

Adverse events by system are listed below.

Haemic & lymphatic

Very common:	leucopenia
Common:	hypochromic anaemia, lymphadenopathy, lymphoma like reaction
Uncommon:	anaemia, blood dyscrasia, coagulation disorder, increased coagulation time, eosinophilia, leukocytosis, lymphocytosis, purpura, thrombocythaemia, thrombocytopenia

Endocrine

Very common:	hypothyroidism
Common:	thyroid disorder
Uncommon:	hyperthyroidism

Metabolic & nutrition

Very common:	hyperlipaemia, hypercholesterolaemia
Common:	increased SGOT, increased SGPT, increased lactic dehydrogenase, increased creatinine, hypoproteinaemia, weight gain
Uncommon:	bilirubinaemia, increased BUN, gout, decreased High Density Lipoprotein

Nervous system

Common:	insomnia, dizziness, hypesthesia
Uncommon:	agitation, ataxia, depression, hyperaesthesia, neuropathy, vertigo

Special senses

Common:	dry eyes, deafness, eye disorder
Uncommon:	abnormal vision, amblyopia, blepharitis, specified cataract, conjunctivitis, corneal lesion, ear disorder, visual field defect

Cardiovascular

Common:	peripheral oedema
Uncommon:	oedema, haemorrhage, hypertension, tachycardia, varicose vein, vasodilatation

Digestive

Common:	nausea, diarrhoea, dry mouth, cheilitis, anorexia, constipation, flatulence, abnormal liver function tests, vomiting
Uncommon:	gastrointestinal disorder, hepatic failure, pancreatitis

Skin & appendages

Very common:	pruritus, rash, exfoliative dermatitis
Common:	dry skin, skin disorder, alopecia, skin ulcer, acne, skin hypertrophy, skin nodule, sweating
Uncommon:	hair disorder, herpes simplex, nail disorder, pustular rash, serous drainage, skin discoloration

Musculoskeletal

Common:	arthralgia, bone pain, myalgia
Uncommon:	myasthenia

Urogenital

Uncommon:	albuminuria, abnormal kidney function

Body as a whole

Very common:	headache, asthenia, pain
Common:	altered hormone level, chills, abdominal pain, allergic reaction, infection
Uncommon:	back pain, cellulitis, fever, parasitic infection, abnormal lab test, mucous membrane disorder, neoplasm

Hyperlipidemia, especially hypertriglyceridemia, was the most common adverse event reported in association with Targretin capsule therapy. For the 84 CTCL patients in the 300 mg/m2/day initial dose group in the MAA submission database, 79% of patients had at least one reported adverse event of hyperlipemia. The severity of hypertriglyceridemia was reduced as the studies progressed and there were no subsequent episodes of pancreatitis following the institution of protocol amendments reducing the initial dose level for the higher dose treatment arm and instituting strict guidelines for the monitoring and management of hyperlipidemia to reduce the risk of additional cases of pancreatitis.
The modifications of dose regimen and the monitoring and management guidelines that effected this improvement in triglyceride levels in the clinical trials are reflected in the guidelines proposed in the SPC (See section 4.4 *Special warnings and special precautions for use*).

The hypothyroidism related to Targretin therapy was easily detected and managed, generally mildly symptomatic until treated, promptly reversible with discontinuation of Targretin capsule therapy, and was not associated with clinical sequelae. Recommendations for the monitoring of thyroid function have been included in the SPC (See section 4.4 *Special warnings and special precautions for use*).

The mechanism for diarrhoea observed in the clinical trials of Targretin is unknown. The incidence of drug-related diarrhoea was low and was directly related to initial dose level, but did not appear to increase substantially until the dose level exceeded the recommended posology of 300 mg/m2/day. Most adverse events of diarrhoea were only mild to moderate in severity. Only 0.7% (1/152) of CTCL patients withdrew from the studies for a primary reason of an adverse event of drug-related diarrhoea. DLTs of diarrhoea were uncommon, dose-related, did not appear to recur after downward dose adjustments, and rarely caused withdrawal from study. Diarrhoea was reported as a DLT in 1.2% (1/84) of patients in the 300 mg/m2/day initial dose group. No CTCL patient treated at the recommended posology experienced a serious adverse event of diarrhoea.
Diarrhoea has been reported as an adverse event in studies of other retinoids, including tretinoin and etretinate.
Mortality from serious coagulopathy was noted in preclinical studies with an oil-based formulation. Dose-limiting toxicities consisting of haemorrhage or events associated with coagulation parameter alterations were rare (2.0%) in CTCL patients and occurred only in the >300 mg/m2/day initial dose group. Serious adverse events of this nature were rare (2.0%) in CTCL patients and each was judged to be not related to Targretin capsule therapy either by the Investigator or upon independent expert review. Determination of haemoglobin should be obtained at baseline, weekly during the first month and then monthly thereafter. Decreases of haemoglobin should be managed according to current medical practice. This has been reflected in the SPC (see section 4.4 *Special warnings and special precautions for use*).

Serious adverse advents

Among all CTCL patients included in the safety update fatal serious adverse events judged to be at least possibly related to study drug were reported in 6.7% (13/193) of patients with CTCL. The only serious adverse events judged related to study drug that occurred in more than one CTCL patient were pancreatitis, pruritus, and pain.
In the main clinical trials serious adverse events considered to be drug related, or possibly related, occurred in 9/152 (6%) of patients with pancreatitis occurring in four patients in association with elevated plasma triglycerides. Pancreatitis was the main serious adverse event related to hyperlipemia. There were no further events of pancreatitis subsequent to the guidelines for the monitoring and management of hyperlipemia, a period of over 12 months. These guidelines are included in the SPC (See section 4.4 *Special warnings and special precautions for use*).
Other serious adverse events included cholestatic jaundice and bilirubinaemia. Adverse events and laboratory abnormalities related to the liver were not common and were nearly exclusively mild to moderate in severity in the studies of Targretin capsules in CTCL. Perhaps the best indication of the level of clinical significance of liver function test abnormalities for patients in the 300 mg/m²/day initial dose group was that there was only one patient (1.2%) withdrawn primarily for liver toxicity (hyperbilirubinemia), and there were no dose-limiting liver toxicities. However, recommendations for the monitoring of hepatic function have been included in the SPC (see section 4.4 *Special warnings and special precautions for use*).

Also seen were diarrhoea, dehydration, herpes zoster, fever, pruritis and chest pain. Seven of the nine patients recovered. One patient died. A second died from Pneumocystis carinii pneumonia after developing cholestatic jaundice and pancreatitis at which time bexarotene was stopped. For this second patient the fatal event was not considered related to the study drug by the investigator. It is not possible to detect from the history given as to whether drug induced leucopenia contributed to this death, but this seems unlikely as death occurred 80 days after discontinuation of bexarotene.
Because of preclinical findings of posterior subcapsular cataracts in rats and dogs, slit-lamp examinations were added to the trial protocols after they started. A high prevalence was noted in the limited pre-study data of 66% for CTCL patients and 58% for non-CTCL patients and the incidence of new cataract formation was 5.2%. Given the high prevalence and natural rate of cataract formation in the older patient population represented in the clinical studies, there was no apparent association between the incidence of lens opacity formation and Targretin capsule administration in the clinical studies. However, an effect of long-term bexarotene treatment on cataract formation has not been excluded and this has been reflected in the SPC (see section 4.4 *Special warnings and special precautions for use*). The Marketing Authorisation Holder has agreed to closely monitor the occurrence of cataract formation, particularly during long term treatment.
Retinoids may cause other types of visual impairment than cataract. It is unknown at this time the degree to which these visual abnormalities may be attributable and selective to RAR binding effects. The Marketing Authorisation Holder has committed to closely monitor visual abnormalities. In the non-CTCL oncology patients serious adverse events occurred in 11/352 (3.1%) of the patients. Pancreatitis occurred in three, hypercalcaemia, pneumonia, and dehydration occurred in two patients each. Other serious adverse events were fever, mucous membrane disorder, diarrhoea, melaena, vomiting, anaemia, increased coagulation time, dyspnoea, confusion, conjunctivitis and haematuria.

Deaths

In study L1069-24 the median duration of time in the study was seven months with a further median five months follow up during which there were 17 deaths in the 107 patients (94 in the original database and a further 13 enrolled after the database cut off). Sixteen of the deaths were considered not related or probably not related by the investigator to bexarotene. One death from bleeding, haemorrhage, coagulopathy and liver failure was considered possibly related.
There were only three deaths among CTCL patients subsequent to the ISS and all were judged to be not related to study medication by the Investigator.
In the non-CTCL oncology patients two deaths in the 352 patients receiving bexarotene monotherapy were considered treatment related. One patient had a prolonged prothrombin time and died of a subdural haematoma. The second patient died of acute pancreatitis associated with elevated triglycerides and continued alcohol abuse.

Discontinuation due to adverse events

Adverse events leading to dose reduction or discontinuation in at least two patients were hyperlipidaemia, neutropenia/leucopenia, diarrhoea, fatigue/lethargy, hypothyroidism, headache, liver function test abnormalities, rash, pancreatitis, nausea, anaemia, allergic reaction, muscle spasm, pneumonia and confusion.

Laboratory findings

In the main efficacy trial, study L1069-24, there was a marked fall in TSH concentrations from a median of 1.60 µU/ml (n=85) at baseline to 0.16 µU/ml at 2-4 weeks (n=39) and 0.37 µU/ml at 12-16 weeks (n=27). Changes in total thyroxine paralleled those of TSH. In the same study there were altered lipid, hepatic and haematology parameters. Abnormalities in aspartate transaminase, with a increase from normal to above the normal range, occurred in 21% of patients at 2-4 weeks in the 300 mg/m^2/day group and 19% in the >300 mg/m^2/day. Triglyceride concentrations became elevated or worsened in 64% of patients (n=94), 28 with concentrations 2.5-5 times the upper limit of normal, 23 with 5-10 times, and nine with >10 times the upper limit. Cholesterol concentrations became elevated or worsened with treatment in 48% of patients, with 21 in the range 7.8-10.3 mmol/l, 14 in the range 10.3-12.9 mmol/l and 13 above 12.9 mmol/l. Leucopenia was common with 30% having a decrease in total leucocyte count and 35% a decrease in neutrophil count to below the normal range by week 4 of treatment. This effect on the white count persisted with treatment. There was also a fall in median haemoglobin from 13.2 g/dl at baseline to 12.1 g/dl at 12-16 weeks.

The most common laboratory toxicities (hyperlipidemia, hypothyroidism and, less frequently, leucopenia) were often asymptomatic, easily monitored and managed with well-tolerated concomitant medications, rarely required treatment discontinuation, reversible upon discontinuation of therapy, and resulted in no clinical sequelae except for pancreatitis (and all four CTCL patients with pancreatitis recovered). Only 2.4% (2/84) of patients at the 300 mg/m²/day initial dose group required Targretin capsules treatment discontinuation because of hypertriglyceridemia, and no patients at this dose required withdrawal from study for a primary reason of hypothyroidism or leucopenia.

Safety in special populations

Patients with diabetes mellitus

Caution should be exercised when administering Targretin capsules in patients using insulin, agents enhancing insulin secretion (e.g. sulfonylureas), or insulin-sensitisers (e.g. thiazolidinediones). Based on the known mechanism of action, Targretin capsules may potentially enhance the action of these agents, resulting in hypoglycaemia. No cases of hypoglycaemia associated with the use of Targretin capsules as monotherapy have been reported.

Other special populations

No specific information is available.
The clinical safety and effectiveness of bexarotene in the paediatric population (below 18 years of age) have not been studied and this product should not be used in a paediatric population until further data become available.
In view of the limited data, patients with renal insufficiency should be monitored carefully while on Targretin capsule therapy. As patients with hepatic insufficiency may theoretically have altered bexarotene pharmacokinetics, they should be monitored carefully while on Targretin capsule therapy

Discussion on clinical safety

In the initial submission, the safety data were presented from 2 CTCL studies (152 patients) and from 9 non-CTCL studies (352 patients). Only 84 CTCL patients and 56 non-CTCL patients were treated with the proposed posology (300 mg/m^2/day).
Later on in the procedure the Marketing Authorisation Holder submitted the safety data collected from 2 CTCL studies (193 patients) and from 9 non-CTCL studies (420 patients); 109 CTCL patients and 57 non-CTCL patients were treated by the recommended posology (300 mg/m^2/day).
Targretin safety profile appears comparable to that of other retinoid drugs, except for leucopenia and hypothyroidism (specific RXR- related effect of Targretin). 97.4% of CTCL patients, and 84.8% of non-CTCL patients experienced drug-related adverse events. The most frequent ones in CTCL patients were hyperlipemia (73%), hypercholesterolemia (37%), hypothyroidism (35%), exfoliative dermatitis + rash (34%), asthenia (28%), leucopenia (28%), headache (26%) and diarrhoea (12%). The majority of these events were dose and duration dependent, requiring a close monitoring during treatment, dose adaptations and/or specific treatment (antilipemic therapy, thyroid hormones replacement). 6.7% of CTCL and 3.1% non-CTCL patients had drug-related serious adverse events. The most frequent drug-related serious adverse events was pancreatitis, secondary to hypertriglyceridemia (12/613 cases); all patients recovered except one who died. There were no further event of pancreatitis subsequent to the introduction of guidelines for the monitoring and management of hyperlipemia.
Whilst the most common toxicities associated with Targretin capsule therapy in patients with CTCL (i.e., hypertriglyceridemia, hypothyroidism, and less frequently, neutropenia) often warranted concurrent pharmacological intervention, the required concomitant therapies were easily administered and monitored. These toxicities were reversible upon Targretin capsule dose reduction, suspension or discontinuation. Guidance for managing these adverse events is provided in the SPC (see section 4.4 *Special warnings and special precautions for use*).
Because of dose-related posterior subcapsular cataracts in rats and dogs, slit-lamp examinations were added to the clinical trial protocols after they started. A high prevalence of cataracts was noted in the limited pre-study data of 66% CTCL and 58% non-CTCL patients and the incidence of new cataract formation was 5.7%. However the follow-up was too short and an effect of long-term bexarotene treatment on cataract formation has not been excluded and will be closely monitored by the Marketing Authorisation Holder. A close monitoring of liver function tests, white blood cells, lipids, thyroid

hormones level is recommended in the SPC (see section 4.4 *Special warnings and special precautions for use)*.
The safety data of long term treatment (> 24 weeks) reveals no new or substantially different safety issues.
Except for hyperlipidemia, adverse events were rarely dose-limiting for patients treated at the recommended posology. For the 84 patients in this initial dose group in the MAA database, hypertriglyceridemia/hypercholesterolemia was dose-limiting for 39% (33/84) patients and neutropenia/leucopenia was dose-limiting for 3.6% (3/84) of patients. No other single toxicity was dose-limiting for more than two patients (2.4%).
Targretin capsule therapy at the recommended posology for patients with CTCL carries substantially less mucocutaneous and nail toxicity and less alopecia than other non-RXR-selective retinoids. Targretin capsules may also cause less myalgias and arthralgias. Lipid elevations are observed with both RAR and RXR-selective retinoids. Central hypothyroidism and, to a lesser extent, leucopenia were reported only for Targretin capsules and appear to be RXR-related effects.

In conclusion, the safety profile of Targretin is close to other retinoids, except for leucopenia and hypothyroidism. The most common treatment-related adverse events were duration dependent.

5. Overall conclusion and benefit-risk assessment

Quality
The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Information has been provided in the dossier demonstrating that the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

Pre-clinical pharmacology and toxicology

Bexarotene is a new synthetic retinoid that binds selectively to three RXR receptors. Overall, the primary pharmacodynamic studies provided adequate evidence that retinoids, including RXR-selective ligands, can modulate T-cell biology, which can have relevance for a possible mechanism of action of bexarotene in CTCL.

Bexarotene was bioavailable following oral administration in both test species. Systemic exposure was decreased upon repeat dosing, which could be attributed to metabolic enzyme induction.

In repeated dose-toxicity studies conducted in rats and in dogs, the target organs of bexarotene were eyes, liver, adrenals and haematological parameters. In rats, bexarotene induced hyperkeratosis and acanthosis of the oesophagus and the non-glandular stomach and follicular atrophy and acanthosis of the skin.

Mortality was observed in both species. Hyperkeratosis of the oesophagus was probably the cause of gavage-related injury leading to an increase of the mortality in treated rats; however, the mechanism of death was not clearly elucidated in treated dogs.

Bexarotene was cataractogenic at dosages comparable to human exposition. The Marketing Authorisation Holder will closely monitor this effect

Bexarotene is teratogenic and embryotoxic at dosages comparable to human exposition. Fertility and peri- and post-natal effects of bexarotene were not evaluated. The use of bexarotene has to be contraindicated during pregnancy. Adequate birth-control measures have to be employed by women of childbearing potential.

Bexarotene is not mutagenic. Carcinogenicity studies have not been performed.

Efficacy

The final recommended dose (300 mg/m^2/day or 516 mg/day) was empirically decided, by decreasing the initial high dose due to toxicity. This dose still seems too high compared to other known retinoids. However, the dose recommendation can be accepted, provided that this dose is adapted according to the safety profile in each individual patient to obtain the most acceptable benefit/risk ratio.

No comparative study was provided. The two pivotal studies were open-label, phase II-III studies in patients with early stage CTCL, and in patients with advanced stage CTCL. Selected population comprised refractory, resistant or intolerant patients, or patients progressing after initial response to 1 or 2 previous treatments. Primary efficacy variable was tumour response to treatment, evaluated by one subjective endpoint (Physicians Global Assessment of clinical condition, PGA) and by one more objective endpoint (Composite Assessment of index lesion disease severity, CA).

The Marketing Authorisation Holder has analysed 193 patients included in both studies; 117 patients refractory to at least 1 systemic treatment were analysed, 24 early stage and 93 advanced stage CTCL patients. The objective response rate in these patients (CA) was 34%.

It can be assumed that the efficacy of Targretin is comparable to that of interferon and of other retinoids in the studied population of patients refractory to at least one systemic treatment. However, the complete responses to Targretin are lower than those observed with other treatments.

For prior irradiation therapies: overall response rates to Targretin (31%) was lower than the response rate for electron beam therapy (72%) and radiotherapy (38%). The response rate to Targretin was superior to those for photopheresis (30%) and PUVA (24%).

No formal studies to investigate the effects of other substances on bexarotene have been conducted. There are indications that bexarotene may induce CYP3A4. Therefore, repeated administration of bexarotene may increase the rate of metabolism and reduce plasma concentrations of other substances metabolised by cytochrome P450 3A4.

There were no formal studies in special patient populations.

Safety

Whilst the most common toxicities associated with Targretin capsule therapy in patients with CTCL (i.e., hypertriglyceridemia, hypothyroidism, and less frequently, neutropenia) often warranted concurrent pharmacological intervention, the required concomitant therapies were easily administered and monitored. These toxicities were reversible upon Targretin capsule dose reduction, suspension or discontinuation.

Because of dose-related posterior subcapsular cataracts in rats and dogs, slit-lamp examinations were added to the clinical trial protocols after they started. A high prevalence of cataracts was noted in the limited pre-study data of 66% CTCL and 58% non-CTCL patients and the incidence of new cataract formation was 5.7%. However the follow-up was too short and an effect of long-term bexarotene treatment on cataract formation has not been excluded and will be closely monitored by the Marketing Authorisation Holder. A close monitoring of liver function tests, white blood cells, lipids, thyroid hormones level is adequately addressed in section 4.4 of the SPC.

The safety data of long term treatment (> 24 weeks) reveals no new or substantially different safety issues.

Caution should be exercised when administering Targretin capsules in patients using insulin, agents enhancing insulin secretion, or insulin-sensitisers. Based on the known mechanism of action, Targretin capsules may potentially enhance the action of these agents, resulting in hypoglycaemia.

In conclusion, the safety profile of Targretin is close to other retinoids, except for leucopenia and hypothyroidism. The most common treatment-related adverse events were duration dependent.

Benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Targretin in the treatment of skin manifestations of advanced stage CTCL patients refractory to at least one systemic treatment was favourable and therefore recommended the granting of the Marketing Authorisation.