SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bexarotene 75 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 75 mg of bexarotene.

Excipient with known effect

Each capsule contains 122.198 mg of sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule.

White to off-white colored dispersion encapsulated in white to off white colored opaque, oblong shape soft gelatin capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bexarotene is indicated for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) in adult patients refractory to at least one systemic treatment.

4.2 Posology and method of administration

Bexarotene therapy should only be initiated and maintained by physicians experienced in the treatment of patients with CTCL.

Posology

The recommended initial dose is 300 mg/m^2/day. Initial dose calculations according to body surface area are as follows:

Table 1 Recommended initial dose

Initial dose level (300 mg/m^2/day)		**Number of 75 mg Bexarotene capsules**
Body Surface Area (m^2)	**Total daily dose (mg/day)**	
0.88 – 1.12	300	4
1.13 - 1.37	375	5
1.38 - 1.62	450	6
1.63 - 1.87	525	7
1.88 - 2.12	600	8
2.13 - 2.37	675	9
2.38 - 2.62	750	10

Dose modification guidelines

The 300 mg/m^2/day dose level may be adjusted to 200 mg/m^2/day then to 100 mg/m^2/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, doses may be carefully readjusted upward. With appropriate clinical monitoring, individual patients may benefit from doses above 300 mg/m^2/day. Doses greater than 650 mg/m^2/day have not been evaluated in patients with CTCL. In clinical trials, bexarotene was administered for up to 118 weeks to patients with CTCL. Treatment should be continued as long as the patient is deriving benefit.

Paediatric population

The safety and efficacy of bexarotene in children (aged below 18 years) have not been established. No data are available.

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 bexarotene cannot be ruled out. The standard dose should be used in the elderly.

Renal impairment

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 bexarotene therapy.

Method of administration

For oral use.

Bexarotene capsule should be taken as a single oral daily dose with a meal. The capsule should not be chewed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

Women of child-bearing potential without effective birth-control measures.

History of pancreatitis.

Uncontrolled hypercholesterolaemia.

Uncontrolled hypertriglyceridaemia.

Hypervitaminosis A.

Uncontrolled thyroid disease.

Hepatic insufficiency.

Ongoing systemic infection.

4.4 Special warnings and precautions for use

General

Bexarotene capsules should be used with caution in patients with a known hypersensitivity to retinoids. No clinical instances of cross-reactivity have been noted. Patients receiving bexarotene should not donate blood for transfusion. Butylated hydroxyanisole, an ingredient in Bexarotene capsule, may cause irritation to the mucous membranes, therefore the capsules must be swallowed intact and not chewed.

Lipids

Hyperlipidaemia has been identified as an effect associated with the use of bexarotene in clinical studies. Fasting blood lipid determinations (triglycerides and cholesterol) should be performed before bexarotene therapy is initiated and at weekly intervals until the lipid response to bexarotene is established, which usually occurs within two to four weeks, and then at intervals no less than monthly thereafter. Fasting triglycerides should be normal or normalised with appropriate intervention prior to bexarotene therapy. Every attempt should be made to maintain triglyceride levels below 4.52 mmol/l in order to reduce the risk of clinical sequelae. If fasting triglycerides are elevated or become elevated during treatment, institution of antilipaemic therapy is recommended, and if necessary, dose reductions (from 300 mg/m^2/day of bexarotene to 200 mg/m^2/day, and if necessary to 100 mg/m^2/day) or treatment discontinuation. Data from clinical studies indicate that bexarotene concentrations were not affected by concomitant administration of atorvastatin. However, concomitant administration of gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene and therefore, concomitant administration of gemfibrozil with bexarotene is not recommended (see section 4.5). Elevations of serum cholesterol should be managed according to current medical practice.

Pancreatitis

Acute pancreatitis associated with elevations of fasting serum triglycerides has been reported in clinical studies. Patients with CTCL having risk factors for

pancreatitis (e.g., prior episodes of pancreatitis, uncontrolled hyperlipidaemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity) should not be treated with bexarotene, unless the potential benefit outweighs the risk.

Liver Function Test (LFT) abnormalities

LFT elevations associated with the use of bexarotene have been reported. Based on data from ongoing clinical trials, elevation of LFTs resolved within one month in 80% of patients following a decrease in dose or discontinuation of therapy. Baseline LFTs should be obtained, and LFTs should be carefully monitored weekly during the first month and then monthly thereafter. Consideration should be given to a suspension or discontinuation of bexarotene if test results reach greater than three times the upper limit of normal values for SGOT/AST, SGPT/ALT, or bilirubin.

Thyroid function test alterations

Changes in thyroid function tests have been observed in patients receiving bexarotene, most often noted as a reversible reduction in thyroid hormone (total thyroxine [total T_4]) and thyroid-stimulating hormone (TSH) levels. Baseline thyroid function tests should be obtained and then monitored at least monthly during treatment and as indicated by the emergence of symptoms consistent with hypothyroidism. Patients with symptomatic hypothyroidism on bexarotene therapy have been treated with thyroid hormone supplements with resolution of symptoms.

Leucopenia

Leucopenia associated with bexarotene therapy has been reported in clinical studies. The majority of cases resolved after dose reduction or discontinuation of treatment. Determination of white blood cell count with differential count should be obtained at baseline, weekly during the first month and then monthly thereafter.

Anaemia

Anaemia associated with bexarotene therapy has been reported in clinical studies. 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.

Psychiatric disorders

Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including bexarotene. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for

appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration.

Lens opacities

Following bexarotene treatment, some patients were observed to have previously undetected lens opacities or a change in pre-existing lens opacities unrelated to treatment duration or dose level of exposure. 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 bexarotene administration. However, an adverse effect of long-term bexarotene treatment on lens opacity formation in humans has not been excluded. Any patient treated with bexarotene who experiences visual difficulties should have an appropriate ophthalmologic examination.

Vitamin A supplementation

Because of the relationship of bexarotene to vitamin A, patients should be advised to limit vitamin A supplements to ≤15,000 IU/day to avoid potential additive toxic effects.

Patients with diabetes mellitus

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

Photosensitivity

The use of some retinoids has been associated with photosensitivity. Patients should be advised to minimise exposure to sunlight and avoid sun lamps during therapy with bexarotene, as *in vitro* data indicate that bexarotene may potentially have a photosensitising effect.

Oral contraceptives

Bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestroprogestive contraceptives. Thus, if treatment with bexarotene is intended in a woman of childbearing potential, a reliable, non-hormonal form of contraception is also required, because bexarotene belongs to a therapeutic class for which the human malformative risk is high.

Paediatric population

Bexarotene is not recommended in children (aged below 18 years).

Excipients

Bexarotene capsule contains sorbitol, therefore patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other substances on bexarotene

No formal studies to evaluate interactions with bexarotene have been conducted. On the basis of the oxidative metabolism of bexarotene by cytochrome P450 3A4 (CYP3A4), coadministration with other CYP3A4 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.

Caution is advised in case of combination with CYP3A4 substrates having a narrow therapeutic margin i.e. immunosuppressive agents (cyclosporine, tacrolimus, sirolimus) as well as CYP3A4-metabolised cytotoxics, i.e. cyclophosphamide, etoposide, finasteride, ifosfamide, tamoxifen, vinca-alcaloids.

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. Under similar conditions, bexarotene concentrations were not affected by concomitant administration of atorvastatin or levothyroxine. Concomitant administration of gemfibrozil with bexarotene is not recommended.

Effects of bexarotene on other substances

There are indications 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, such as tamoxifen. For example bexarotene may reduce the efficacy of oral contraceptives (see sections 4.4 and 4.6).

Bexarotene may potentially enhance the action of insulin, agents enhancing insulin secretion (e.g. sulfonylureas), or insulin-sensitisers (e.g. thiazolidinediones), resulting in hypoglycaemia
(see section 4.4).

Laboratory test interactions

CA125 assay values in patients with ovarian cancer may be accentuated with bexarotene therapy.

Food interactions

In all clinical trials, patients were instructed to take bexarotene 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 bexarotene 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.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data from the use of bexarotene in pregnant women. 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 (see section 5.3). Bexarotene is contraindicated in pregnancy (see section 4.3).

If this medicinal product is used inadvertently during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be informed of the potential hazard to the foetus.

Contraception in males and females

Women of childbearing potential must use adequate birth-control measures when bexarotene is used. A negative, sensitive, pregnancy test (e.g. serum beta-human chorionic gonadotropin, beta-HCG) should be obtained within one week prior to bexarotene therapy. Effective contraception must be used from the time of the negative pregnancy test through the initiation of therapy, during therapy and for at least one month following discontinuation of therapy.

Whenever contraception is required, it is recommended that two reliable forms of contraception be used simultaneously. Bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestroprogestative contraceptives (see section 4.5). Thus, if treatment with bexarotene is intended in a woman with childbearing potential, a reliable, non-hormonal contraceptive method is also recommended. Male patients with sexual partners who are pregnant, possibly pregnant, or may potentially become pregnant must use condoms during sexual intercourse while taking bexarotene and for at least one month after the last dose.

Breastfeeding

It is unknown whether bexarotene is excreted in human milk. Bexarotene should not be used in breastfeeding mothers.

Fertility

There are no human data on the effect of bexarotene on fertility. In male dogs, some effects have been documented (see section 5.3). Effects on fertility cannot be excluded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness and visual difficulties have been reported in patients taking bexarotene. Patients who experience dizziness or visual difficulties during therapy must not drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The safety of bexarotene has been examined in clinical studies of 193 patients with CTCL who received bexarotene for up to 118 weeks and in 420 non-CTCL cancer patients in other studies.

In 109 patients with CTCL treated at the recommended initial dose of 300 mg/m^2/day, the most commonly reported adverse reactions to bexarotene were hyperlipaemia ((primarily elevated triglycerides) 74%), hypothyroidism (29%), hypercholesterolaemia (28%), headache (27%), leucopenia (20%), pruritus (20%), asthenia (19%), rash (16%), exfoliative dermatitis (15%), and pain (12%).

Tabulated list of adverse reactions

The following bexarotene-related adverse reactions were reported during clinical studies in patients with CTCL (N=109) treated at the recommended initial dose of 300 mg/m^2/day. The frequencies of adverse reactions are classified as very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1,000 to <1/100), rare (>1/10,000 to <1/1,000), and very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse reactions reported in patients in clinical trials

System Organ Class (MedDRA terminology)	**Very Common**	**Common**	**Uncommon**
Blood and lymphatic system disorders	Leucopenia	Lymphoma Like Reaction Lymphadenopathy Hypochromic Anaemia[1,2,3]	Blood Dyscrasia Purpura Coagulation Disorder Coagulation Time Increased[2,3] Anaemia[1] Thrombocytopenia[3] Thrombocythemia Eosinophilia[1] Leukocytosis[2] Lymphocytosis
Endocrine disorders	Hypothyroidism	Thyroid Disorder	Hyperthyroidism
Metabolism and nutrition disorders	Hyperlipaemia Hypercholesterolaemia	Weight Gain SGOT Increased SGPT Increased Lactic	Gout Bilirubinemia[1,3] BUN Increased[1] High Density

		Dehydrogenase Increased Creatinine Increased Hypoproteinaemia	Lipoprotein Decreased
Nervous system disorders		Dizziness Hypesthesia Insomnia	Ataxia Neuropathy Vertigo Hyperaesthesia Depression [1, 2, 3] Agitation
Eye disorders		Dry Eyes Eye Disorder	Cataract Specified[1,2,3] Amblyopia[3] Visual Field Defect Corneal Lesion Abnormal Vision[1,2,3] Blepharitis Conjunctivitis[3]
Ear and labyrinth disorders		Deafness	Ear disorder
Cardiac disorders			Tachycardia
Vascular disorders		Peripheral Oedema	Haemorrhage Hypertension Oedema[3] Vasodilatation[1,2,3] Varicose Vein
Gastrointestinal disorders		Vomiting Diarrhoea[1,3] Nausea[3] Anorexia[1] Liver Function Tests Abnormal Cheilitis[2] Dry Mouth[2,3]	Pancreatitis[1,3] Hepatic Failure Gastrointestinal Disorder[1]

		Constipation Flatulence	
Skin and subcutaneous tissue disorders	Exfoliative Dermatitis Pruritus Rash	Skin Ulcer Alopecia[1] Skin Hypertrophy Skin Nodule Acne Sweating Dry Skin[2,3] Skin Disorder	Serous Drainage[1] Herpes Simplex Pustular Rash Skin Discoloration[3] Hair Disorder[1] Nail Disorder[1,3]
Musculoskeletal and connective tissue disorders		Bone Pain Arthralgia Myalgia	Myasthaenia[1]
Renal and urinary disorders			Albuminuria[1,3] Kidney Function Abnormal
General disorders and administration site conditions	Pain Headache Asthaenia	Allergic Reaction Infection Chills[1] Abdominal Pain Hormone Level Altered[1]	Neoplasm Fever[1,2,3] Cellulitis Infection Parasitic Mucous Membrane Disorder[3] Back Pain[1,2,3] Lab Test Abnormal

1. Adverse reactions noted with increased frequency when bexarotene was administered at a dose >300mg/m^2/day.
2. Adverse reactions noted with increased frequency when bexarotene was administered at a dose of 300 mg/m^2/day in non-CTCL cancer patients.
3. Adverse reactions noted with increased frequency when bexarotene was administered at a dose of >300 mg/m^2/day (compared to administration to CTCL patients at 300 mg/m^2/day) in non-CTCL cancer patients.

Additional adverse reactions observed when used outside of the recommended dose and indication (i.e. used in CTCL at an initial dose >300mg/m^2/day or in non-CTCL cancer indications):

Newly observed adverse reactions

Ecchymosis, petechia, abnormal white blood cells, thromboplastin decreased, abnormal erythrocytes, dehydration, increased gonadotrophic luteinizing hormone, weight loss, increased alkaline phosphatase, increased creatinine phosphokinase, lipase increased, hypercalcaemia, migraine, peripheral neuritis, paraesthesia, hypertonia, confusion, anxiety, emotional lability, somnolence, decreased libido, nervousness, night blindness, nystagmus, lacrimation disorder, tinnitus, taste perversion, chest pain, arrhythmia, peripheral vascular disorder, generalized oedema, haemoptysis, dyspnoea, increased cough, sinusitis, pharyngitis, dysphagia, mouth ulceration, oral moniliasis, stomatitis, dyspepsia, thirst, abnormal stools, eructation, vesicobullous rash, maculopapular rash, leg cramps, haematuria, flu syndrome, pelvic pain, and body odour.

Single observations of the following were also reported: bone marrow depression, decreased prothrombin, decreased gonadotrophic luteinizing hormone, increased amylase, hyponatraemia, hypokalaemia, hyperuricaemia, hypocholesterolaemia, hypolipaemia, hypomagnesaemia, abnormal gait, stupor, circumoral paraesthesia, abnormal thinking, eye pain, hypovolaemia, subdural haematoma, congestive heart failure, palpitation, epistaxis, vascular anomaly, vascular disorder, pallor, pneumonia, respiratory disorder, lung disorder, pleural disorder, cholecystitis, liver damage, jaundice, cholestatic jaundice, melaena, vomiting, laryngismus, tenesmus, rhinitis, increased appetite, gingivitis, herpes zoster, psoriasis, furunculosis, contact dermatitis, seborrhoea, lichenoid dermatitis, arthritis, joint disorder, urinary retention, impaired urination, polyuria, nocturia, impotence, urine abnormality, breast enlargement, carcinoma, photosensitivity reaction, face oedema, malaise, viral infection, enlarged abdomen.

The majority of adverse reactions were noted at a higher incidence at doses greater than 300 mg/m^2/day. Generally, these resolved without sequelae on dose reduction or withdrawal of treatment. However, among a total of 810 patients, including those without malignancy, treated with bexarotene, there were three serious adverse reactions with fatal outcome (acute pancreatitis, subdural haematoma and liver failure). Of these, liver failure, subsequently determined to be not related to bexarotene, was the only one to occur in a CTCL patient.

Hypothyroidism generally occurs 4-8 weeks after commencement of therapy. It may be asymptomatic and responds to treatment with thyroxine and resolves upon withdrawal of treatment.

Bexarotene has a different adverse reaction profile to other oral, non-retinoid X receptor (RXR)-selective retinoids. Owing to its primarily RXR-binding activity, bexarotene is less likely to cause mucocutaneous, nail, and hair

toxicities; arthralgia; and myalgia; which are frequently reported with retinoic acid receptor (RAR) -binding agents.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No clinical experience with an overdose of bexarotene has been reported. Any overdose should be treated with supportive care for the signs and symptoms exhibited by the patient.

Doses up to 1000 mg/m^2/day of bexarotene have been administered in clinical studies with no acute toxic effects. Single doses of 1500 mg/kg (9000 mg/m^2) and 720 mg/kg (14,400 mg/m^2) were tolerated without significant toxicity in rats and dogs, respectively.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents.

ATC code: L01XF03.

Mechanism of action

Bexarotene is a synthetic compound that exerts its biological action through selective binding and activation of the three RXRs: α, 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 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.

Clinical efficacy and safety

Bexarotene capsules were evaluated in clinical trials of 193 patients with CTCL of whom 93 had advanced stage disease refractory to prior systemic therapy. Among the 61 patients treated at an initial dose of 300 mg/m^2/day, the overall response rate, according to a global assessment by the physician, was 51% (31/61) with a clinical complete response rate of 3%. Responses were also determined by a composite score of five clinical signs (surface area, erythema, plaque elevation, scaling and hypo/hyperpigmentation) which also considered all extracutaneous CTCL manifestations. The overall response rate according to this composite assessment was 31% (19/61) with a clinical complete response rate of 7% (4/61).

5.2 Pharmacokinetic properties

Absorption

Absorption/dose proportionality: pharmacokinetics were linear up to a dose of 650 mg/m^2. Terminal elimination half-life values were generally between one and three hours. Following repeat once daily dose administration at dose levels $\geq$ 230 mg/m^2, C_{max} and AUC in some patients were less than respective single dose values. No evidence of prolonged accumulation was observed. At the recommended initial daily-dose level (300 mg/m^2), single-dose and repeated daily-dose bexarotene pharmacokinetic parameters were similar.

Distribution

Protein binding/distribution: bexarotene is highly bound (>99%) to plasma proteins. The uptake of bexarotene by organs or tissues has not been evaluated.

Biotransformation

Metabolism: bexarotene metabolites in plasma include 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. *In vitro* studies suggest glucuronidation as a metabolic pathway, and 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

Excretion: 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. Renal excretion is not a significant elimination pathway for bexarotene.

Other special populations

Age

Based on the population pharmacokinetic analysis of data for 232 patients aged ≥ 65 years and 343 patients aged < 65 years, age has no statistically significant effect on bexarotene pharmacokinetics.

Body weight and gender

Based on the population pharmacokinetics analysis of data for 614 patients with a weight range of 26 to 145 kg, the bexarotene apparent clearance increases with increasing body weight. Gender has no statistically significant effect on bexarotene pharmacokinetics.

Race

Based on the population pharmacokinetic analysis of data for 540 Caucasian and 44 Black patients, bexarotene pharmacokinetics are similar in Blacks and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of bexarotene for other races.

5.3 Preclinical safety data

Bexarotene is not genotoxic. Carcinogenicity studies have not been conducted. Fertility studies have not been conducted; however, in sexually immature male dogs, reversible aspermatogenesis (28-day study) and testicular degeneration (91-day study) were seen. When bexarotene was administered for six months

to sexually mature dogs, no testicular effects were seen. Effects on fertility cannot be excluded. Bexarotene, in common with the majority of retinoids, was teratogenic and embryotoxic in an animal test species at systemic exposures that are achievable clinically in humans. Irreversible cataracts involving the posterior area of the lens occurred in rats and dogs treated with bexarotene at systemic exposures that are achievable clinically in humans. The aetiology of this finding is unknown. An adverse effect of long-term bexarotene treatment on cataract formation in humans has not been excluded.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Polyethylene glycol 400,
Polysorbate 20,
Povidone,
Butylated hydroxyanisole.

Capsule shell

Gelatin,
Sorbitol special-glycerin blend (glycerin, sorbitol, sorbitol anhydrides (1,4-sorbitan), mannitol and water),
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

Keep the bottle tightly closed.

6.5 Nature and contents of container

High-density polyethylene bottles with child-resistant closures containing 100 capsules.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Limited
Dashwood House, 69 Old Broad Street,
London, EC2M 1QS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 12762/0686

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