

- 1. NAME OF THE MEDICINAL PRODUCT.** Targretin 75 mg soft capsules
- 2. QUALITATIVE AND QUANTITATIVE COMPOSITION.** Each capsule contains 75 mg of bexarotene. For a full list of excipients, see section 6.1.
- 3. PHARMACEUTICAL FORM.** Soft capsule. Off-white capsule, containing a liquid suspension and imprinted with “Targretin”.
- 4. CLINICAL PARTICULARS. 4.1 Therapeutic indications.** Targretin capsules are indicated for the treatment of skin manifestations of advanced stage cutaneous. T-cell lymphoma (CTCL) 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. The recommended initial dose is 300 mg/m²/day. Targretin capsules should be taken as a single oral daily dose with a meal (see section 4.5). Initial dose calculations according to body surface area are as follows:

| Initial dose level (300 mg/m ² /day) | | Number of 75 mg Targretin 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/m²/day dose level may be adjusted to 200 mg/m²/day then to 100 mg/m²/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/m²/day. Doses greater than 650 mg/m²/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. *Use in children and adolescents:* 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. *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 bexarotene 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 bexarotene therapy.

4.3 Contraindications. Known hypersensitivity to bexarotene or to any of the excipients of the product. 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: Targretin 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 Targretin, 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/m²/day of bexarotene to 200 mg/m²/day, and if necessary to 100 mg/m²/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 T₄]) 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. *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 oestrogenic 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. **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 5 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, vincaalkaloids. 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/m²/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). *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 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. **4.6 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. 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 oestrogenic 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. *Lactation*: it is not known whether bexarotene is excreted in human milk. Bexarotene should not be used in breast-feeding mothers.

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 Targretin. Patients who experience dizziness or visual difficulties during therapy must not drive or operate machinery. **4.8 Undesirable effects**

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/m²/day, the most commonly reported adverse reactions to Targretin 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%). The following Targretin-related adverse reactions were reported during clinical studies in patients with CTCL (N=109) treated at the recommended initial dose of 300 mg/m²/day. The frequencies of adverse reactions are classified as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Very common: Leucopenia

Common: Lymphoma Like Reaction, Lymphadenopathy, Hypochromic Anaemia^{1,2,3},

Uncommon: Blood Dyscrasia, Purpura, Coagulation Disorder, Coagulation Time Increased^{2,3},

Anaemia¹, Thrombocytopenia³, Thrombocytopenia, Eosinophilia¹,

Leukocytosis², Lymphocytosis

Endocrine disorders

Very common: Hypothyroidism

Common: Thyroid Disorder

Uncommon: Hyperthyroidism

Metabolism and nutrition disorders

Very common: Hyperlipaemia, Hypercholesterolaemia

Common: Weight Gain, SGOT Increased, SGPT Increased, Lactic Dehydrogenase

Increased, Creatinine Increased, Hypoproteinaemia,

Uncommon: Gout, Bilirubinemia^{1,3}, BUN Increased¹, High Density Lipoprotein Decreased

Nervous system disorders

Common: Dizziness, Hypesthesia, Insomnia

Uncommon: Ataxia, Neuropathy, Vertigo, Hyperaesthesia, Depression^{1,2,3}, Agitation

Eye disorders

Common: Dry Eyes, Eye Disorder

Uncommon: Cataract Specified^{1,2,3}, Amblyopia³, Visual Field Defect, Corneal Lesion,

Abnormal Vision^{1,2,3}, Blepharitis, Conjunctivitis³

Ear and labyrinth disorders

Common: Deafness

Uncommon: Ear disorder

Cardiac disorders

Uncommon: Tachycardia

Vascular disorders

Common: Peripheral Oedema

Uncommon: Haemorrhage, Hypertension, Oedema³, Vasodilatation^{1,2,3}, Varicose Vein

Gastrointestinal disorders

Common: Vomiting, Diarrhoea^{1,3}, Nausea³, Anorexia¹, Liver Function Tests Abnormal, Cheilitis², Dry Mouth^{2,3}, Constipation, Flatulence,

Uncommon: Pancreatitis^{1,3}, Hepatic Failure, Gastrointestinal Disorder¹

Skin and subcutaneous tissue disorders

Very common: Exfoliative Dermatitis, Pruritus, Rash

Common: Skin Ulcer, Alopecia¹, Skin Hypertrophy, Skin Nodule, Acne, Sweating, Dry Skin^{2,3}, Skin Disorder

Uncommon: Serous Drainage¹, Herpes Simplex, Pustular Rash, Skin Discoloration³ Hair Disorder¹, Nail Disorder^{1,3}

Musculoskeletal and connective tissue disorders

Common: Bone Pain, Arthralgia, Myalgia

Uncommon: Myasthenia¹

Renal and urinary disorders

Uncommon: Albuminuria^{1,3}, Kidney Function Abnormal

General Disorders and administration site conditions

Very common: Pain, Headache, Asthenia

Common: Allergic Reaction, Infection, Chills¹, Abdominal Pain, Hormone Level Altered¹

Uncommon: Neoplasm, Fever^{1,2,3}, Cellulitis, Infection Parasitic, Mucous Membrane Disorder³, Back Pain^{1,2,3}, Lab Test Abnormal

1: adverse reactions noted with increased frequency when bexarotene was administered at a dose >300mg/m²/day.

2: adverse reactions noted with increased frequency when bexarotene was administered at a dose of 300 mg/m²/day in non-CTCL cancer patients.

3: adverse reactions noted with increased frequency when bexarotene was administered at a dose of >300 mg/m²/day (compared to administration to CTCL patients at 300 mg/m²/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/m²/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, hypolipidaemia, 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/m²/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.

4.9 Overdose. No clinical experience with an overdose of Targretin 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/m²/day of bexarotene have been administered in clinical studies with no acute toxic effects. Single doses of 1500 mg/kg (9000 mg/m²) and 720 mg/kg (14,400 mg/m²) were tolerated without significant toxicity in rats and dogs, respectively.

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients. Capsule content: macrogol, polysorbate, povidone, butylated hydroxyanisole. Capsule shell: gelatin, sorbitol special-glycerin blend (glycerin, sorbitol, sorbitol anhydrides (1,4-sorbitan), mannitol and water) titanium dioxide (E171) printing ink (SDA 35A alcohol (ethanol & ethyl acetate), propylene glycol (E1520), iron oxide black (E172), polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400, ammonium hydroxide 28%)

5.2 Incompatibilities. Not applicable.

5.3 Shelf life. 3 years

5.4 Special precautions for storage. Do not store above 30°C. Keep the bottle tightly closed.

5.5 Nature and contents of container. High-density polyethylene bottles with child-resistant closures containing 100 capsules.

5.6 Special precautions for disposal and other handling. No special requirements.

6. MARKETING AUTHORISATION HOLDER

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7. MARKETING AUTHORISATION NUMBER. EU/1/01/178/001

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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9. DATE OF REVISION OF THE TEXT