Toctino®▼ (alitretinoin)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Toctino®▼ 10mg soft capsules.

Toctino®▼ 30mg soft capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 10mg or 30mg of alitretinoin.

This medicinal product contains the excipients soya-bean oil and sorbitol.

For a full list of excipients, see section 6.1 "List of excipients".

3. PHARMACEUTICAL FORM

Soft capsule.

The Toctino 10mg capsule is an opaque brown soft capsule imprinted with "A1" in white.

The Toctino 30mg capsule is an opaque red-brown soft capsule imprinted with "A3" in white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Toctino is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.

Patients in whom the eczema has predominantly hyperkeratotic features are more likely to respond to treatment than in those in whom the eczema predominantly presents as pompholyx (See section 5.1 "Pharmacodynamic properties").

4.2 Posology and method of administration

Toctino should only be prescribed by dermatologists, or physicians with experience in the use of systemic retinoids who have full understanding of the risks of systemic retinoid therapy and monitoring requirements. Prescriptions of Toctino for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of Toctino should occur on the same day. Dispensing of Toctino should occur within a maximum of 7 days of the prescription.

The recommended dose range for Toctino is 10mg-30mg once daily.

The recommended start dose for Toctino is 30mg once daily. A dose reduction to 10mg once daily may be considered in patients with unacceptable adverse reactions to the higher dose. In studies investigating 10mg and 30mg daily doses, both doses resulted in clearing of the disease. The 30mg dose provided a more rapid response and a higher response rate. The 10mg daily dose was associated with fewer adverse events (see section 4.4 "Special warnings and precautions for use" and section 5.1 "Pharmacodynamic Properties").

A treatment course of Toctino may be given for 12 to 24 weeks depending on response. Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of treatment. In the event of relapse, patients may benefit from further treatment courses of Toctino.

The capsules should be taken with a meal once daily.

Toctino should not be prescribed if the patient's eczema can be adequately controlled by standard measures, including skin protection, avoidance of allergens and irritants, and treatment with potent topical corticosteroids.

Children

Toctino is not recommended for use in patients under 18 years of age.

4.3 Contraindications

Pregnancy is an absolute contraindication to treatment with Toctino (see section 4.6 "Pregnancy and lactation").

Toctino is contraindicated in woman of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4 "Special warnings and special precautions for use").

Toctino contains soya oil. Patients who are allergic to peanut, soya or with rare hereditary fructose intolerance should not take this medicine.

Toctino is contraindicated in breastfeeding.

Toctino is also contraindicated in patients

- With hepatic insufficiency
- With severe renal insufficiency
- With uncontrolled hypercholesterolaemia
- With uncontrolled hypertriglyceridaemia
- With uncontrolled hypothyroidism
- With hypervitaminosis A
- With hypersensitivity either to alitretinoin, to other retinoids or to any of the excipients, in particular in case of allergies to peanut or soya
- Receiving concomitant treatment with tetracyclines (see section 4.5 "Interactions with other medicinal products and other forms of interactions")

4.4 Special warnings and precautions for use

Pregnancy Prevention Programme

This medicinal product is **TERATOGENIC**.

Toctino is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- She understands the teratogenic risk
- She understands the need for rigorous follow-up, on a monthly basis
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the duration of treatment and 1 month after the end of treatment. At least one and preferably two complementary forms of contraception including a barrier method should be used
- Even if she has amenorrhoea she must follow all of the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of Toctino

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions
- The patient has used at least one and preferably two methods of effective contraception including a barrier method for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment
- Negative pregnancy test results have been obtained before, during and 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception.

As a minimum requirement, female patients at potential risk of pregnancy must use at least one effective method of contraception. Preferably the patient should use two complementary forms of contraception including a barrier method. Contraception should be continued for at least 1 month after stopping treatment with Toctino, even in patients with amenorrhea.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mIU/mL are recommended to be performed in the first 3 days of the menstrual cycle, as follows:

One month prior to starting therapy

In order to exclude the possibility of pregnancy prior to starting contraception, it is recommended that an initial medically supervised pregnancy test should be performed and its date and result recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception.

At the start of therapy

A medically supervised pregnancy test should also be performed during the consultation when Toctino is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. This test should ensure the patient is not pregnant when she starts treatment with Toctino.

Follow-up visits

Follow-up visits should be arranged at 28 day intervals. The need for repeated medically supervised pregnancy tests every month should be determined in consideration amongst other of the patient's sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhea). Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment

Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

Prescribing and dispensing restrictions

Prescriptions of Toctino for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of Toctino should occur on the same day. Dispensing of Toctino should be completed within a maximum of 7 days of the prescription.

Male patients

Small amounts of alitretinoin have been detected in the semen of healthy volunteers receiving 40 mg of alitretinoin and there is no indication of drug accumulation in semen. Assuming complete vaginal absorption of these amounts would have a negligible effect on the endogenous plasma levels of the female partner and therefore does not appear to pose a risk to the foetus if the partner is pregnant. Based on non-clinical findings, male fertility may be compromised by treatment with Toctino (see section 5.3 "Preclinical safety data").

Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month following discontinuation of Toctino because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material

In order to assist prescribers, pharmacists and patients in avoiding foetal exposure to alitretinoin, the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of Toctino, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Psychiatric disorders

Depression, aggravated depression, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with systemic retinoids. Particular care needs to be taken in patients with a history of depression and patients on alitretinoin treatment should therefore be observed for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of alitretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

UV light

The effects of UV light are enhanced by retinoid therapy, therefore patients should avoid excessive exposure to sunlight and the unsupervised use of sun lamps. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.

Patients who experience dryness of the skin and lips should be advised to use a skin moisturising ointment or cream and a lip balm.

Musculo-skeletal and connective tissue disorders

Treatment with other systemic retinoids has been associated with bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments.

Myalgia, arthralgia and increased serum creatinine phosphokinase values have been observed in patients treated with alitretinoin.

Eye disorders

Treatment with alitretinoin has been associated with dry eyes. The symptoms usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient wearing glasses during treatment.

Treatment with systemic retinoids has been associated with corneal opacities and keratitis. Decreased night vision has been observed in patients treated with alitretinoin. These effects usually resolve after discontinuation of therapy.

Patients experiencing visual difficulties should be referred to an ophthalmologist. Withdrawal of alitretinoin may be necessary.

Benign intracranial hypertension

Treatment with systemic retinoids, including alitretinoin, has been associated with the occurrence of benign intracranial hypertension, some of which involved concomitant use of tetracyclines (see section 4.3 "Contraindications" and section 4.5 "Interaction with other medicinal products and other forms of interaction"). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop signs of benign intracranial hypertension should discontinue alitretinoin immediately.

Lipid Metabolism

Alitretinoin has been associated with an increase in plasma cholesterol and triglyceride levels. Serum cholesterol and triglycerides (fasting values) should be monitored.

Alitretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8 "Undesirable effects"). Triglyceride levels in excess of 800mg/dL (9mmol/L) are sometimes associated with acute pancreatitis, which may be fatal.

Thyroid function

Changes in thyroid function tests have been observed in patients receiving alitretinoin, most often noted as a reversible reduction in thyroid stimulating hormone (TSH) levels and T4 (free thyroxine).

Hepatobiliary disorders

Treatment with other systemic retinoids has been associated with transient and reversible increases in liver transaminases. In the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

Gastrointestinal disorders

Systemic retinoids have been associated with IBD (inflammatory bowel disease, including regional ileitis) in patients without a history of intestinal disorders. If severe diarrhoea is observed, diagnosis of IBD should be considered and alitretinoin should be discontinued immediately.

Allergic reactions

Anaphylactic reactions have been rarely reported in systemic retinoids, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

High risk patients

In patients with diabetes, obesity, cardiovascular risk factors or a lipid metabolism disorder undergoing treatment with alitretinoin, more frequent checks of serum values for lipids may be necessary. It is recommended that these patients are started with 10mg once daily and titrated up to the maximum dose of 30mg if necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

Alitretinoin is metabolised by cytochrome P450 3A4 (CYP3A4).

Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

Co-administration with CYP3A4 inhibitors such as ketoconazole increases the plasma level of alitretinoin and dose reduction may be required. The effects of other inhibitors of CYP3A4 have not been studied. Alitretinoin did not affect the pharmacokinetics of ketoconazole.

A 16% reduction of simvastatin plasma levels was observed when co-administered with alitretinoin.

The effects on other similar medicinal products have not been studied. Simvastatin did not affect the pharmacokinetics of alitretinoin.

No pharmacokinetic interactions were observed when alitretinoin was co-administered with ciclosporin or the oral contraceptive ethinyl estradiol and norgestimate.

Pharmacodynamic interactions

Patients should not take vitamin A or other retinoids as concurrent medication due to the risk of hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumour cerebri) have been reported with concomitant use of retinoids and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see sections 4.3 "Contraindications" and section 4.4 "Special warnings and precautions for use").

4.6 Pregnancy and lactation

Pregnancy is an absolute contraindication to treatment with Toctino (see section 4.3, "Contraindications"). If pregnancy does occur in spite of the pregnancy prevention precautions during treatment with Toctino or in the month following discontinuation of therapy, there is a great risk of very severe and serious malformation of the foetus.

Alitretinoin is a retinoid and therefore is a potent teratogen. The foetal malformations associated with exposure to retinoids include central nervous system abnormalities (hydrocephalus, cerebellar malformation/ abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.

If pregnancy occurs in a woman treated with Toctino, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Lactation

Alitretinoin is highly lipophilic, therefore the passage of alitretinoin into human milk is very likely. Due to the potential risk for the exposed child, the use of alitretinoin is contraindicated during breastfeeding.

Fertility

Small amounts of alitretinoin have been detected in the semen of healthy volunteers receiving 40mg of alitretinoin and there is no indication of drug accumulation in semen. In the event of complete vaginal absorption of these amounts, this would have a negligible effect on the endogenous plasma levels of the female partner and therefore does not appear to pose a risk to the foetus if the partner is pregnant. Based on non-clinical findings, male fertility may be compromised by treatment with Toctino (see section 5.3 "Preclinical safety data").

4.7 Effects on ability to drive and use machines

Decreased night vision has been reported in patients treated with alitretinoin and other retinoids. Patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

4.8 Undesirable effects

The most frequent adverse drug reactions (ADRs) observed under alitretinoin therapy are headache (30mg: 21%; 10mg: 11%), flushing (30mg: 5.9%; 10mg: 1.6%), and laboratory changes consisting of increased levels of triglycerides (30mg: 35.4%; 10mg: 17.0%), increased cholesterol (30mg: 27.8%; 10mg: 16.7%), decreased levels of thyroid stimulating hormone (TSH, 30mg: 8.4%; 10mg: 6.0%) and decreased levels of free T4 (30mg: 10.5%; 10mg: 2.9%). These reversible ADRs are dose dependent and may therefore be alleviated by dose reduction.

	Very common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1000, < 1/100)	Rare (≥ 1/10,000, < 1/1000)
Blood and lymphatic system disorders		Anaemia, increased iron binding capacity, monocytes decreased; thrombocytes increased		
Endocrine Disorders		TSH decreased, free T4 decreased		
Nervous system disorders	Headache			Benign intracranial hypertension
Eye disorders		Conjunctivitis, dry eye, eye irritation	Blurred vision, cataract	
Vascular disorders		Flushing		Vasculitis
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Hepatobiliary disorders		Transaminase increased[1)]		
Skin and subcutaneous tissues disorders		Dry skin, dry lips, cheilitis, eczema[1)], dermatitis[1)], erythema, alopecia	Pruritus, rash, skin exfoliation, asteatotic eczema	
Musculo-skeletal and connective tissue disorders		Arthralgia[1)], myalgia[1)]	Exostosis, (hyperostosis), ankylosing spondylitis	
Investigations	Hypertriglyceridemia, high density lipoprotein decreased, hypercholesterolemia	Blood creatinine phosphokinase increased		

[1)] The incidence of adverse events was not higher than those observed in the corresponding placebo group.

Psychiatric effects, in particular depression, and mood changes and suicidal ideation, have been associated with retinoids. In clinical studies, where patients with a history or active psychiatric disorders were excluded patients have been monitored for depression using the CES-D (Center for Epidemiological Studies - Depression) score. Treatment with alitretinoin was not associated with changes in the CES-D score.

The following adverse events have not been observed in clinical trials with alitretinoin, but have been observed with other retinoids: inflammatory bowel disease, diabetes mellitus, colour blindness (colour vision deficiencies), and contact lens intolerance (see section 4.4 "Special warnings and precautions for use").

Changes in bone mineralisation and extra-osseous calcifications have been associated with systemic retinoid treatment. In clinical studies with alitretinoin, degenerative changes of the spine and ligamentous calcifications were frequent findings in patients with chronic hand eczema before treatment (baseline), with minor progression in a small number of patients during treatment. These observations were consistent with age dependent degenerative changes. Assessments of bone density (DXA) did not indicate a dose dependent effect on bone mineralisation.

4.9 Overdose

Alitretinoin is a derivative of vitamin A. Alitretinoin has been administered in oncological clinical studies at dosages of more than 10 times the therapeutic dosage given for chronic hand eczema. The adverse effects observed were consistent with retinoid toxicity, and included severe headache, diarrhoea, facial flushing, hypertriglyceridaemia. These effects were reversible.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: D11AX19

Mechanism of action

The pharmacological action of retinoids may be explained by their effects on cell proliferation, cell differentiation, apoptosis, angiogenesis, keratinisation, sebum secretion and immunomodulation. Unlike other retinoids, which are specific agonists of either RAR or RXR receptors, alitretinoin binds to members of both receptor families. The mechanism of action of alitretinoin in chronic hand eczema is unknown. Alitretinoin has demonstrated immunomodulatory and anti-inflammatory effects that are relevant to skin inflammation. CXCR3 ligands and CCL20 chemokines, expressed in eczematous skin lesions, are down-regulated by alitretinoin in cytokine-stimulated keratinocytes and dermal endothelial cells. In addition, alitretinoin suppresses the expansion of cytokine-activated leucocyte subsets and antigen presenting cells.

It has been observed that in humans alitretinoin only minimally affects sebum secretion.

Clinical efficacy

The safety and efficacy of Toctino in patients with severe chronic hand eczema (CHE) refractory to topical corticosteroids has been established in two randomised, double blind, placebo-controlled Phase 3 studies.

The primary endpoint in these studies was the proportion of patients achieving Physicians Global Assessment (PGA) ratings of clear or almost clear hands at the end of therapy. The treatment duration was 12 to 24 weeks.

The BACH (Benefit of Alitretinoin in Chronic Hand Dermatitis Study) included 1032 severe CHE patients who had no response or a transient response (initial improvement and worsening of disease despite continued treatment) to potent topical corticosteroids or who were intolerant of potent topical corticosteroids. All phenotypes of CHE were included: hyperkeratosis (87%), pompholyx (27%), fingertip dermatitis (43%), and other (15%). Essentially all patients had signs of skin inflammation, comprising of erythema and/or vesicles. Treatment with alitretinoin led to a significantly higher proportion of patients with clear/almost clear hands, compared to placebo. The response was dose dependent (see Table 2). Response rates for different CHE subtypes were also dose dependent, except for patients with pompholyx (see Table 3).

Table 2: Primary Efficacy Parameter - Results

	Alitretinoin		
Primary Endpoint	**10 mg**	**30 mg**	**Placebo**
ITT Population	**N=418**	**N=409**	**N=205**
PGA at end of study			
Total Response Rate	115 (27.5%)	195 (47.7%)	34 (16.6%)
Clear	39 (9.3%)	90 (22.0%)	6 (2.9%)
Almost clear	76 (18.2%)	105 (25.7%)	28 (13.7%)
Comparison to placebo	P=0.004	P=<0.001	N/A

Table 3: Response rate by CHE subtype

CHE subtype (% of ITT population)	Hyperkeratotic (64%)	Hyperkeratotic/ Pompholyx (22%)	Pompholyx (5%)
Response rate (PGA)	30mg: 54% 10 mg: 30% Placebo: 12%	30mg: 33% 10 mg: 23% Placebo: 12%	30mg: 33% 10 mg: 22% Placebo: 30%

Secondary endpoints included the proportion of patients achieving at least mild disease, time to achieving clear to almost clear hands, reduction in total lesion symptom score, patient global assessment (PaGA) of disease severity, reduction in extent of disease (see Table 4). Patients with clear/almost clear hands at end of treatment were followed up for 24 weeks. During that period no active drug treatment for CHE was allowed. Relapse was defined as 75% of the initial total lesion symptom score.

Table 4: Secondary Efficacy Parameters - Results

	Alitretinoin		
Efficacy Variable	**10 mg**	**30 mg**	**Placebo**
ITT Population	**N=418**	**N=409**	**N=205**
Partial Response Rate (clear, almost clear or mild disease)	207 (49.5%)	254 (62.1%)	74 (36.1%)
PaGA (clear or almost clear)	101 (24.2%)	163 (39.9%)	31 (15.1%)
mTLSS (mean % change from baseline)	-50.79 (n=411)	-60.80 (n=408)	-37.30 (n=204)
Extent of disease (mean % change from baseline)	-40.01 (n=402)	-54.15 (n=391)	-31.93 (n=197)

The numbers of responding patients without observed relapse at the end of the 24-weeks follow-up period is given in Table 5 below. In this analysis, the majority of responders given 10mg and 30mg alitretinoin did not relapse by the end of the follow-up period.

Table 5: Relapse Rates* at the End of Follow-up

	Alitretinoin		Placebo N=205
	10 mg N=418	**30 mg N=409**	
Responders	115 (100%)	195 (100%)	34 (100%)
No Relapse	81 (70.4%)	122 (62.6%)	19 (55.9%)

* Corresponds to a last-observation-carried-forward (LOCF) computation

A follow-up study (the second Phase 3 study) investigated the efficacy and safety of a second course of treatment both in patients who previously responded (Cohort A) and in patients who did not (Cohort B). Cohort A patients who responded in the previous study but who relapsed were randomised to the same dose they received in their initial treatment (10 or 30mg) or to placebo in a 2:1 ratio. 80% of relapsing patients who again received the 30 mg dose achieved clear/almost clear hands vs. 8% of the corresponding placebo group ($p<0.001$). 48% of relapsing patients who again received the 10 mg dose achieved clear/almost clear hands vs. 10% of the corresponding placebo group ($p=0.1$). Patients who responded to treatment with placebo in the previous study also received placebo in this follow-up study. Many of these patients responded again to treatment with placebo (69.2%).

5.2 Pharmacokinetic Properties

Absorption

The absorption of alitretinoin from the gastro-intestinal tract is variable and dose-proportional over the therapeutic range from 10-30mg. The absolute bioavailability of alitretinoin has not been determined. When alitretinoin is taken with food, the systemic exposure is enhanced by a factor of 4 and the variability of exposure is decreased. Therefore, alitretinoin should be taken with a meal.

Distribution

Alitretinoin strongly binds to plasma proteins. The volume of distribution of alitretinoin in man has not been determined, but animal studies indicate a volume of distribution greater than the extracellular volume.

Metabolism

Alitretinoin is metabolised by oxidation in the liver by CYP3A4 isoenzymes into 4-oxo-alitretinoin. Both compounds undergo isomerisation into all-trans retinoic acid and 4-oxo-all-trans retinoic acid. After oral administration, the contribution of the metabolites in plasma to the systemic exposure of alitretinoin is approximately 35% to 80% for 4-oxo-alitretinoin. The major metabolite 4-oxo-alitretinoin is further glucuronidated and eliminated in urine. Alitretinoin is degraded similarly to vitamin A by sequential cleavage of the carbon-side chain.

During a 12-to 24-week treatment period with 10 or 30mg, the exposure to alitretinoin remained stable.

Elimination

Alitretinoin is an endogenous retinoid. Alitretinoin concentrations return to normal range within 1 to 3 days after treatment cessation.

Excretion of radio-labelled alitretinoin was complete with approximately 94% of the dose recovered. Radio-labelled material was eliminated mainly in urine and a smaller fraction (approx. 30%) in faeces. The most abundant excretion compound is the glucuronide of 4-oxo-alitretinoin amounting to 6.5% of the dose in urine.

Elimination half-life of unchanged alitretinoin ranges between 2 to 10 hours. Alitretinoin and its 4-oxo-metabolite do not accumulate.

Pharmacokinetic in special populations

In a pharmacokinetic study in patients, gender, weight and age did not affect the pharmacokinetics of alitretinoin.

The pharmacokinetics of alitretinoin in CHE patients was similar to that in healthy volunteers.

Alitretinoin kinetics have not been studied in patients with hepatic or with severe renal insufficiency or in patients below 18 years (see section 4.3).

5.3 Preclinical safety data

Acute toxicity

As with other retinoids, the acute toxicity of alitretinoin was low in mice and rats. The LD50 after intraperitoneal administration was >4000 mg/kg after 24 hours and 1400 mg/kg after 10 days. The approximate LD50 after oral administration in rats was 3000 mg/kg.

Chronic toxicity

Alitretinoin was tested in long-term studies up to 9 months in dogs and 6 months in rats. Signs of toxicity were dose-related and occurred at exposures similar to the human therapeutic exposure based on AUC. Effects were characteristic for retinoids (consistent with hypervitaminosis A), and were generally spontaneously reversible.

Teratogenicity

Like other retinoids, alitretinoin has been shown to be teratogenic *in vitro* and *in vivo*.

Due to the teratogenic potential of alitretinoin, women of childbearing potential must adhere to strict pregnancy prevention measurers during and 1 month following alitretinoin therapy (see section 4.3 “Contraindications”, section 4.4 “Special warnings and special precautions for use” and section 4.6 “Pregnancy and lactation”).

Fertility

Alitretinoin was tested in a study of fertility and early embryonic development in rats. No effects on male or female reproductive parameters were observed at the highest dose tested. However, systemic exposure in this study did not reach the level observed in patients.

As with other retinoids reversible effects on male reproductive organs were observed in experimental animals in the form of disturbed spermatogenesis and associated degenerative lesions of the testes. The safety margin in dogs with regard to the no-effect level of toxicity to male reproductive organs was 1-6 for a human dose of 30mg.

Mutagenicity

In *in vitro* or *in vivo* tests, alitretinoin has been shown not to be mutagenic.

Carcinogenicity

Alitretinoin was tested in 2-year carcinogenicity studies in rats and mice. Dose-related retinoid-specific toxicity was seen at higher doses, but no carcinogenic potential was noted.

Phototoxicity

Alitretinoin was found to be phototoxic *in vitro* and *in vivo*.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Capsule content:

Soya-bean oil, refined

Partially hydrogenated soya-bean oil

Triglycerides, medium chain

Beeswax, yellow

All-rac-α-tocopherol

Capsule shell:

Gelatin

Glycerol

Sorbitol, liquid (non-crystallising)

Water purified

Iron oxide (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package. Keep the blister in the outer carton to protect from light.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminum or COC (cycloolefin copolymer)/Aluminum blisters. Pack sizes of 30 capsules.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Basilea Medical Ltd, 14/16 Frederick Sanger Road, The Surrey Research Park, Guildford, Surrey GU2 7YD

8. MARKETING AUTHORISATION NUMBER

10mg, 30 capsules PL 32205/0001-0001

30mg, 30 capsules PL 32205/0001-0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 SEPTEMBER 2008.

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