SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Toctino 10 mg capsules, soft

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, soft contains 10 mg of alitretinoin

Excipients with known effect:
Soya-bean oil. Each 10 mg capsule contains 176.50 mg soya-bean oil.

Sorbitol. Each 10 mg capsule contains 20.08 mg sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft

Brown oval capsule approximately 11 mm in length and 7 mm in width marked with "A1".

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 those in whom the eczema predominantly presents as pompholyx (see section 5.1).

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.

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

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

Duration of treatment
A treatment course of Toctino may be given for 12 to 24 weeks depending on response. Discontinuation of therapy is recommended in patients who have achieved clear or almost clear hands earlier than 24 weeks (see section 5.1). Discontinuation of therapy should also be considered for patients who still have severe disease after the initial 12 weeks of continuous treatment.

Retreatment
In the event of relapse, patients may benefit from further treatment courses of Toctino (see section 5.1).

Method of administration
The capsules should be taken with a main meal once daily, preferably at the same time each day (see section 5.2).

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.

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

Renal impairment
Toctino is contraindicated in patients with severe or end stage renal impairment (see section 4.3).

Toctino is not recommended for use in patients with moderate renal impairment as there is insufficient data (see section 5.2).

No alteration of dosage or dosing frequency is required in patients with mild renal impairment (see section 5.2).

Hepatic impairment
Toctino is contraindicated in patients with hepatic impairment (see section 4.3).

Elderly
No alteration of dosage and dosing frequency is required in patients over 65 years (see section 5.2).

4.3 Contraindications

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

Toctino is contraindicated in woman of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4).

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 nursing mothers.

Toctino is also contraindicated in patients

- With hepatic insufficiency
- With severe renal insufficiency
- With uncontrolled hypercholesterolemia
- With uncontrolled hypertriglyceridemia
- With uncontrolled hypothyroidism
- With hypervitaminosis A
- With hypersensitivity either to alitretinoin, to other retinoids or to any of the excipients listed in section 6.1, in particular in case of allergies to peanut or soya
- Receiving concomitant treatment with tetracyclines (see section 4.5).

4.4 Special warnings and precautions for use

4.4 Special warnings and precautions for use

Teratogenic effects
Toctino is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.
Toctino is strictly contraindicated in:
- Pregnant women
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

Pregnancy Prevention Programme
This medicinal product is **TERATOGENIC.**

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

- Toctino is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids (see section 4.1).
- The potential for pregnancy must be assed for all female patients.
- 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 entire duration of treatment and for 1 month after the end of treatment. At least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception should be used.
- Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.
- Even if she has amenorrhoea she must follow all of the advice on effective contraception.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.
- She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of alitretinoin.

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 understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, 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 1 month after the end of treatment. The dates and results of pregnancy tests should be documented.

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.

If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the foetus. The risk persists until the product has been completely eliminated, which is within one month following the end of treatment.

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. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional.

As a minimum requirement, female patients of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent form), or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 1 month after stopping treatment with Toctino, even in patients with amenorrhoea.

Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL are recommended to be performed, as follows:

Prior to starting therapy
At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with alitretinoin.

Follow-up visits
Follow-up visits should be arranged at regular intervals, ideally monthly. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity, recent menstrual history (abnormal menses, missed periods or amenorrhoea) and method of contraception. 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
1 month after stopping treatment, women should undergo a final pregnancy test.

Prescribing and dispensing restrictions
For women of childbearing potential, the prescription duration of alitretinoin should ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of alitretinoin should occur on the same day.

This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication.

Male patients
The available data suggests that the level of maternal exposure from the semen of patients receiving Toctino, is not of a sufficient magnitude to be associated with teratogenic effects of Toctino. Based on non-clinical findings, the male fertility may be compromised by treatment with Toctino (see section 5.3).

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 alitretinoin 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 alitretinoin, 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, depression aggravated, 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, including alitretinoin (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Prior to initiation of Toctino and at each visit during therapy, patients should be asked about any psychiatric disorder, depression, or mood disturbance. Patients should stop Toctino if they develop depression, mood disturbance, psychosis, or aggression. However, discontinuation of Toctino may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary. Awareness by family or friends may be useful to detect mental health deterioration.

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.

Skin and subcutaneous tissues disorders
Patients who experience dryness of the skin and lips should be advised to use a skin moisturizing 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 creatine 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 to wear 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 and section 4.5). 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.

Pancreatitis
Toctino should be discontinued if symptoms of pancreatitis occur (see section 4.8). Triglyceride levels in excess of 800 mg/dL (9 mmol/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, including alitretinoin, have been associated with 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 and/or blood glucose may be necessary.

Sorbitol
Toctino capsules contain sorbitol. 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

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Pharmacokinetic interaction
Alitretinoin is metabolised by cytochrome P450 (CYP) 2C9, CYP2C8, CYP3A4 and undergoes isomerisation.

Concomitant medications that may affect the pharmacokinetics of alitretinoin
Co-administration with CYP3A4 inhibitors such as ketoconazole increases the plasma level of alitretinoin and therefore dose reduction to 10 mg should be considered. The effects of other inhibitors of CYP3A4 have not been studied.
A reduction in dose to 10 mg should be considered when alitretinoin is co-administered with potent CYP2C9 inhibitors (e.g. fluconazole, miconazole, oxandrolone) or potent CYP2C8 inhibitors (e.g. gemfibrozil).

Simvastatin did not affect the pharmacokinetics of alitretinoin.

No pharmacokinetic interactions were observed when alitretinoin was co-administered with ciclosporin.

Effect of alitretinoin on the pharmacokinetics of concomitant medications
Alitretinoin may increase the exposure of CYP2C8 substrates; therefore co-administration with amiodarone (a CYP2C8 substrate with a long half-life and narrow therapeutic index) is not recommended. Caution should be used if alitretinoin is co-administered with other medications that are substrates for CYP2C8 (e.g. paclitaxel, rosiglitazone, repaglinide).

Decreases of <25 % in simvastatin and simvastatin acid plasma levels were observed when co-administered with alitretinoin. The effects on other similar medicinal products have not been studied.

Alitretinoin did not affect the pharmacokinetics of ketoconazole or ciclosporin.

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 (pseudotumor cerebri) have been reported with concomitant use of retinoids and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see sections 4.3 and section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy is an <u>absolute</u> contraindication to treatment with Toctino (see section 4.3). 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 specialized or experienced in teratology for evaluation and advice.

Breast-feeding
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 in nursing mothers.

Fertility
Small amounts of alitretinoin (above endogenous levels) have been detected in the semen of some healthy volunteers receiving 40 mg of alitretinoin and drug accumulation in semen is not expected. Assuming complete vaginal absorption of these amounts, this would have a negligible effect on the endogenous plasma levels of the female partner or a foetus 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).

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

4.8 Undesirable effects

The safety and efficacy of Toctino in patients with severe chronic hand eczema (CHE) unresponsive to treatment with potent topical corticosteroids has been evaluated in two randomised, double blind, placebo-controlled clinical studies (see section 5.1).

The most frequent adverse drug reactions (ADRs) observed under alitretinoin therapy are headache (30 mg: 23.9%; 10 mg: 10.8%), erythema (30 mg: 5.5%; 10 mg: 1.7%), nausea (30 mg: 5.1%; 10 mg: 2.4%), flushing (30 mg: 5.9%, 10 mg: 1.6%), and laboratory changes consisting of increased levels of triglycerides (30 mg: 35.4%; 10 mg: 17.0%), increased cholesterol (30 mg: 27.8%; 10 mg: 16.7%), decreased levels of thyroid stimulating hormone (TSH, 30 mg: 8.4%, 10 mg: 6.0%) and decreased levels of free T4 (30 mg: 10.5%; 10 mg: 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)**	**Very Rare (<1/10000)**	**Unknown**
Blood and lymphatic system disorders		Anaemia, increased iron binding capacity, monocytes decreased; thrombocytes increased				
Immune system disorders						Anaphylactic reactions, hypersensitivity
Endocrine Disorders		TSH decreased, free T4 decreased				
Psychiatric disorders				Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations	Suicide, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour	
Nervous system disorders	Headache	Dizziness		Benign intracranial hypertension		
Eye disorders		Conjunctivitis, dry eye, eye irritation	Blurred vision, cataract			Decreased night vision
Ear and labyrinth disorders		Tinnitus				
Vascular disorders		Flushing, hypertension		Vasculitis		

	Very common (≥ 1/10)	**Common (≥ 1/100 < 1/10)**	**Uncommon (≥ 1/1000, < 1/100)**	**Rare (≥ 1/10,000 < 1/1000)**	**Very Rare (<1/10000)**	**Unknown**
Respiratory, thoracic and mediastinal disorders			Epistaxis			
Gastrointestinal disorders		Nausea, dry mouth, vomiting	Dyspepsia			Inflammatory bowel disease
Hepatobiliary disorders		Transaminase increased[1)]				
Skin and subcutaneous tissues disorders		Dry skin, dry lips, cheileitis, eczema[1)], dermatitis[1)], erythema, alopecia	Pruritus, rash, skin exfoliation, asteatotic eczema	Nail disorders, photosensitivity reaction, hair texture changes		
Musculo-skeletal and connective tissue disorders		Arthralgia[1)], myalgia[1)]	Exostosis, (hyperostosis), ankylosing spondylitis			
General disorders and administration site conditions		Fatigue				Peripheral oedema
Investigations	Hypertriglyceridemia, high density	Blood creatinine phosphokinase increased				

	Very common (≥ 1/10)	Common (≥ 1/100 < 1/10)	Uncommon (≥ 1/1000, < 1/100)	Rare (≥ 1/10,000 < 1/1000)	Very Rare (<1/10000)	Unknown
	lipoprotein decreased, hypercholesterolaemia					

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

The following adverse events have not been observed in clinical trials with alitretinoin, but have been observed with other retinoids: diabetes mellitus, colour blindness (colour vision deficiencies), and contact lens intolerance (see section 4.4).

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.

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 of the therapeutic dosage given for chronic hand eczema. The adverse effects observed were consistent with retinoid toxicity, and included severe headache, diarrhoea, facial flushing, hypertriglyceridemia. These effects were reversible.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other dermatologicals

ATC code: D11AH04

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. Alitretinoin suppresses the production of chemokines that are involved in recruitment of leukocytes to sites of skin inflammation, reduces expansion of T lymphocytes and antigen-presenting cells, and inhibits effect on cell differentiation. 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 leucocytes 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) unresponsive to treatment with potent topical corticosteroids has been evaluated 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 (see Table 1). The treatment duration was 12 to 24 weeks.

The BAP00089 study (BACH) was conducted in Europe and Canada, and 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 were intolerant of potent topical corticosteroids. All phenotypes of CHE were included; approximately 30% of patients had hyperkeratotic only CHE, however the majority of patients had multiple phenotypes. 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 1).

Secondary endpoints included the proportion of partial responders (patients achieving at least mild disease), time to response (achieving clear to almost clear hands), reduction in modified total lesion symptom score (mTLSS), patient global assessment (PaGA) of disease severity, and reduction in extent of disease (see Table 1).

The second study, BAP001346 (HANDEL) was conducted in the US and included 596 with severe CHE 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. Subjects were considered unresponsive if they had severe CHE after at least 2 weeks of treatment

with a very potent topical corticosteroid during a 16-week run-in period. All phenotypes of CHE were included.

Secondary endpoints included estimated median time to response (time from the start of randomised study treatment to first PGA assessment of clear or almost clear), reduction in modified total lesion symptom score (mTLSS), patient global assessment (PaGA) of disease severity, and reduction in extent of disease at end of therapy (see Table 1).

Table 1 Results: Primary and Key Secondary Endpoints

	BAP00089 (BACH)			**BAP01346 (HANDEL)**	
Primary Endpoint	10 mg	30 mg	Placebo	30 mg	Placebo
ITT Population	N = 418	N = 409	N = 205	N = 298	N = 298
PGA at end of treatment n (%)					
Total Response	115 (27.5%)	195 (47.7%)	34 (16.6%)	118 (39.6%)	44 (14.8%)
Clear	39 (9.3%)	90 (22.0%)	6 (2.9%)	58 (19.5%)	14 (4.7%)
Almost Clear	76 (18.2%)	105 (25.7%)	28 (13.7%)	60 (20.1%)	30 (10.1%)
Comparison to Placebo[a]	P = 0.004	P <0.001	NA	P <0.001	NA
Secondary Endpoints					
PaGA at the end of treatment n (%)					
Clear or Almost Clear	101 (24.2%)	163 (39.9%)	31 (15.1%)	117 (39.3%)	41 (13.8%)
Comparison to Placebo[a]	P = 0.013	P <0.001	NA	P <0.001	NA
Percent Change from Baseline mTLSS at the end of treatment					
Mean (STD)	-50.79 (36.13)	-60.80 (38.58)	-37.30 (37.65)	-53.99 (40.16)	-29.86 (37.83)
Median	-56.25	-75.0	-38.68	-67.70	-24.40
Min – Max	-100 – 66.7	-100 – 175	-100 – 72.7	-100 – 60	-100 – 63.6
Comparison to Placebo[b]	P <0.001	P <0.001	NA	P <0.001	NA
Percent Change from Baseline in Extent of Disease at the end of treatment					
Mean (STD)	-40.01 (49.57)	-54.15 (46.89)	-31.93 (45.56)	-46.56 (53.75)	-24.20 (48.21)
Median	-50.0	-75.0	-33.33	-62.50	-18.20
Min – Max	-100 – 200	-100 – 140	-100 – 130	-100 – 166.7	-100 – 140
Comparison to Placebo[b]	P = 0.016	P <0.001	NA	P <0.001	NA
Median Time to Response for Responders at the end of treatment					
Median (Days)	115.0	85.0	141	65.0	117.0
Comparison to Placebo[c]	P = 0.01	P <0.001	NA	P <0.001	NA
Partial Response Rate (clear, almost clear, or mild disease)					

N (%)	207 (49.5%)	254 (62.1%)	74 (36.1%)	NA	NA

a: From pairwise continuity corrected chi-square tests versus placebo based on proportion of responders.
b: From non-parametric Kruskal Wallis test versus placebo based on mean change from baseline.
c: From Log Rank Test versus placebo based on median time to response.

Duration of treatment
A longitudinal dose response analysis of Phase 3 studies (BAP00089, BAP001346, & BAP00091 – Cohort A) showed that once subjects had clear or almost clear hands, there was no relationship between the duration of treatment and the likelihood of relapse. Therefore, discontinuation of therapy is recommended in patients who have achieved clear or almost clear hands earlier than 24 weeks (see section 4.2). In the pivotal clinical studies 67% of subjects who responded to alitretinoin treatment did not return to severe disease 24 weeks after stopping treatment and therefore would not be candidates for retreatment within that time period.

Retreatment
A retreatment study (BAP00091 – Cohort A) investigated the efficacy and safety of a second course of treatment in patients who previously responded to treatment in the BAP00089 study, but who relapsed. Patients were randomised to the same dose they received in their initial treatment (10 or 30 mg) or to placebo in a 2:1 ratio. (N=70 alitretinoin, N=47 placebo). Results suggest that patients who previously responded to alitretinoin treatment may benefit from retreatment.

5.2 Pharmacokinetic properties

5.2 Pharmacokinetic properties

Absorption

Alitretinoin is a low solubility, low permeability compound with a low and variable bioavailability. Alitretinoin is not consistently absorbed from the gastrointestinal tract in fasted state. The systemic exposure is substantially (>2-fold) enhanced when taken with a high-fat meal.

In vitro data from a gastrointestinal system suggest the amount of alitretinoin available for absorption differs with fat intake (when given with an approximately 25% fat meal, the amount available for absorption is less than when given with ~40% or ~60% fat meal). Therefore, alitretinoin should be administered with a main meal once daily, preferably at the same time of day to maximise exposure.

After administration of alitretinoin 30 mg once daily with a meal containing approximately 40% fat, the median T_{max} is 4 hours, the average C_{max} is 177 ng/mL, and the average $AUC_{(0-\square)}$ is 405 ng*hr/mL.

Peak plasma concentrations (C_{max}) and exposure (AUC) of alitretinoin increase with increasing single doses over the range of 5 to 150 mg. AUC values of alitretinoin

increases proportionally with dose for once daily doses of 10 mg to 30 mg. The C_{max} of alitretinoin may increase less than proportionally with increasing dose.

Distribution
Alitretinoin is 99.1% bound to plasma proteins. The volume of distribution of alitretinoin is estimated to be greater than the extracellular volume (>14L), but less than total body water.

Metabolism
Alitretinoin is metabolised by CYP2C9, CYP2C8, and CYP3A4 isoenzymes to form 4-oxo-alitretinoin. Both compounds undergo isomerisation into tretinoin (or isotretinoin) and their 4-oxo metabolites. After oral administration of alitretinoin 4-oxo-alitretinoin is the main observed active circulating metabolite with an AUC which accounts for >70% of the AUC of the parent drug. The isomers of alitretinoin (tretinoin, isotretinoin) and 4-oxo-alitretinoin (4-oxo-tretinoin and 4-oxo-isotretinoin) are minor accounting for <12% of exposure of parent drug. 4-oxo-alitretinoin is further glucuronidated and eliminated in urine.

There are no consistent time-dependent changes (neither induction nor accumulation) in the pharmacokinetics of alitretinoin or its measured metabolites

Elimination
Alitretinoin is an endogenous retinoid. Alitretinoin concentrations return to endogenous levels within 2 to 3 days after treatment cessation.

Excretion of a radio-labelled dose of alitretinoin was complete, with approximately 94% of the dose recovered within 14 days. Radio-labelled material was eliminated mainly in urine as metabolites (63%, with <1% as unchanged parent drug) with a smaller fraction (approx. 30% with 1% as unchanged parent drug) in faeces. The most abundant excretion compound is the glucuronide of 4-oxo-alitretinoin amounting to 6.5% of the dose in urine.

The elimination half-life averaged 9 hours for alitretinoin and 10 hours for 4-oxo-alitretinoin.

Pharmacokinetic in special populations
The pharmacokinetics of alitretinoin and its measured metabolites in special populations (obesity, gender, age, and renal impairment) were evaluated in a study in 32 subjects with moderate to severe CHE receiving alitretinoin for 12 to 24 weeks. These analyses showed:

Obesity
Increased body weight or body mass index (BMI) does not result in clinically significant changes in alitretinoin or 4-oxo-alitretinoin exposure.

Gender
There are no clinically significant gender-related differences in alitretinoin or 4-oxo-alitretinoin AUC and Cmax.

Elderly
While the pharmacokinetic data in elderly subjects is limited (n=6 over 60 years of age and n=3 over 65 years of age), there does not appear to be a relationship between increasing age and the dose-normalized AUC or Cmax of alitretinoin or 4 oxo-alitretinoin.

A longitudinal dose-response model from clinical efficacy studies shows that elderly subjects (n=126) have an earlier and more pronounced response to treatment and are less likely to relapse, but are more likely to experience elevated triglyceride levels after 12 to 16 weeks of treatment.

Renal Impairment
While pharmacokinetic data in subjects with moderate renal impairment is not available, the pharmacokinetics of alitretinoin is not affected by mild renal impairment, with an average AUC of 342 (range: 237-450) and 312 (195-576) ng*h/mL in those with an estimated creatinine clearance 60-90 mL/min (n=8) or ≥ 90 mL/min (n=23), respectively normalised to an alitretinoin 30 mg dose. The C_{max} and $AUC_{(0\text{-}tau)}$ of 4-oxo-alitretinoin may be slightly higher in subjects with mild renal impairment, although the effect is small (< 20%).

No data are available in subjects with severe renal impairment (CrCl <30 mL/min) or end stage renal disease.

Hepatic Impairment
A pharmacokinetic study conducted in 8 subjects with liver cirrhosis and Child-Pugh Class A (mild, n=6) or B (moderate, n=2) and in 8 gender, age, height and weight-matched healthy subjects shows that there are no clinically relevant differences between patients with hepatic impairment and healthy subjects in the C_{max} (mean± standard deviation [SD]: 101 ± 40 ng/mL vs 144±40 ng/mL, respectively) or AUC (mean±SD: 248 ± 116 ng/mL vs 314 ± 86 ng/mL, respectively) of alitretinoin. The C_{max} (mean± SD: 30± 20 ng/mL vs 56 ± 25 ng/mL, respectively) and AUC (mean±SD: 162± 82 ng/mL vs 219 ± 49 ng/mL, respectively) of 4-oxo-alitretinoin are lower in patients with hepatic impairment.

There are no data available in subjects with severe hepatic impairment and limited data in patients with moderate hepatic impairment.

Alitretinoin kinetics has not been studied in patients below 18 years.

5.3 Preclinical safety data

Acute toxicity
As with other retinoids, the acute toxicity of alitretinoin was low in mice and rats. The LD_{50} after intraperitoneal administration was >4000 mg/kg after 24 hours and 1400 mg/kg after 10 days. The approximate LD_{50} 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, section 4.4 and section 4.6).

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 which reached similar plasma concentrations as those observed in humans. 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 30 mg.

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 PARTICULARS

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, red (E172)
Iron oxide, black (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminum blisters. Pack sizes of 30 capsules, soft.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline UK Limited
79 New Oxford Street
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WC1A 1DG
United Kingdom

Trading as Stiefel

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