Public Assessment Report

Scientific discussion

TOCTINO
Alitretinoin

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This module reflects the scientific discussion for the approval of Toctino. The procedure was finalised at July 30, 2008. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Denmark granted marketing authorisation to Basilea Ltd. on July 30, 2008 for the medicinal product Toctino (applied for as Datiros) 10 mg and 30 mg soft gelatine capsules in the treatment of 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. The product is prescription-only medicine.

The application was submitted in accordance with Article 8(3) of Directive 2001/83/EC (i.e. dossier with administrative, quality, pre-clinical and clinical data), known active substance as it was approved in the central procedure on October 11, 2000, in the form of a 0.1% gel for topical treatment of cutaneous Karposi's sarcoma, currently marketed in several countries (not in DK).

Since this is a very different indication and route of administration, alitretinoin cannot be considered as having well-established medicinal use for the purposes of the present application. Therefore, the Applicant has submitted the results of a number of non-clinical and clinical studies.

Scientific advice for this product was given by the RMS on November 30, 2005 and on March 06, 2007. Generally the applicant followed the RMS advice.

No pediatric development program is available for this medicinal product.

The applicant has provided a detailed description of a pharmacovigilance system which fulfils the requirements.

The safety profile of alitretinoin is similar to other oral retinoids. The identified and potential safety concerns have been included in the SPC, and safety concerns will be monitored with routine pharmacovigilance activities. To minimize the risk of teratogenicity, the applicant has proposed a risk minimization plan which include extensive pregnancy testing before, during and 5 weeks after termination of therapy, educational material for physicians, pharmacists and patients (Pregnancy Prevention Program), and limitations in pack size. All failures of the PPP will be analysed in a root cause analysis.

An Environmental Risk Assessment Report has been provided which includes all phases, tiers and compartments stipulated in the applicable CHMP guideline. The outcome of this exercise indicates that alitretinoin does not represent a risk to the aquatic environment, including ground water, and is unlikely to lead to significant bioaccumulation in fish. The risk ratios for sediment and soil cannot be calculated, however, as there are no experimental data on the effects of alitretinoin on sediment and soil dwelling organisms.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Most non-clinical safety studies were conducted in accordance with GLP regulations. The remaining studies were conducted to acceptable quality standards.

All clinical trials were conducted in accordance with GCP and other applicable guidelines. No regulatory CHMP guidelines specific to chronic hand eczema are available at the moment.

Problem statement
Chronic hand eczema or chronic hand dermatitis is a prevalent condition with multifactorial aetiologies that may be the end stage of a number of different dermatological diseases, such as irritant or allergic contact dermatitis, endogenous vesicular hand eczema (pompholyx), atopic hand eczema, frictional dermatitis and endogenous hyperkeratotic eczema in the middle-aged.
Chronic hand eczema is irrespectively of the causative factors characterized by the classic signs and symptoms of eczema including pruritus, pain, erythema, oedema, vesiculation, hyperkeratosis and fissures.

Treatment of chronic hand eczema usually requires long-term or intermittent therapy with potent corticosteroids in addition to continuous use of emollients and avoidance of any relevant provoking allergens or irritants. Patients who are refractory to potent corticosteroids may obtain remission by off-label use of other immunosuppressants such as prednisolone, azathioprine, methotrexate, ciclosporin A or mycophenolate mofetil. Other alternative treatment options include photo therapy with either UVB or PUVA. A subset of patients presenting with hyperkeratotic eczema (eczema hyperkeratoticum, eczema climacteriale, seen in middle-aged males and females, may only benefit from off-label treatment with an oral retinoid, usually retinoid.

It can be concluded that only few approved therapies are available for patients with chronic hand eczema and that new safe and effective treatment modalities are highly needed.

About the product
Alitretinoin (9-cis retinoic acid) is an endogenous metabolite of vitamin A. Alitretinoin belongs to the chemical class of retinoids among which isotretinoin (13-cis retinoic acid) is approved and marketed in both a topical and oral formulation for treatment of acne vulgaris and acitretin is approved and marketed for treatment of psoriasis vulgaris.

The pharmacological action of retinoids may be explained by their effects on cell proliferation, cell differentiation, apoptosis, angiogenesis, keratinization, sebum secretion and immunomodulation. Alitretinoin binds to RARs and the so-called retinoid X receptors (RXRs).

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.

II. QUALITY ASPECTS

II.1 Introduction
Toctino red-brown soft gelatine capsules contain 10 or 30 mg of alitretinoin. The product contains soy-bean oil and sorbitol. The container system is defined as PVC/PE/PVDC/Aluminum or COC (cycloolefin copolymer)/Aluminum blisters.

A pack size of 30 capsules has been approved.

II.2 2.2 Drug Substance
The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Toctino 10 and 30 mg soft gelatine capsules are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. The batch analysis results show that the finished products meet the specifications proposed.

Furthermore the process is regarded a non-standard process which requires validation data up front the Marketing Authorization.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

Accepted shelf-life and storage condition are 3 years at 'no special storage precaution' but 'Keep container in outer packaging as the product is sensitive to light'.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Primary pharmacodynamics included in-vitro studies of nuclear receptor binding, chemokine gene expression, leukocyte subset expansion and human keratinocyte and sebaceous cell proliferation. In-vivo studies were limited to assays for comedolytic activity in the rhino mouse utricle reduction assay, sebaceous gland size in hamster ears and repair of photo damaged skin in UVB-irradiated mice following topical administration only. Overall, alitretinoin behaved similar to other retinoids in most assays, except nuclear receptor binding and activation. In the latter assay, alitretinoin and tretinoin bound to RAR with IC_{50} values in the 5-17 nM range whereas only alitretinoin and, to a lesser extent, its 4-oxo metabolite, bound to RXR, with IC_{50} values of 70-95 and 830-1000 nM, respectively. Alitretinoin, tretinoin, isotretinoin and, to a lesser extent, their 4-oxo metabolites, all caused RAR activation, with EC_{50} values ranging from 3-18 and from 8-61 nM, respectively, whereas alitretinoin and its metabolite also caused RXR activation, with EC_{50} values ranging from 5-720 and from 90-620 nM respectively, and alitretinoin was 5 times as potent as tretinoin in this regard. The clinical impact of this finding is poorly understood, therefore proof of concept must be provided through clinical studies.

Since alitretinoin is approved throughout Europe as a topical treatment for Kaposi's sarcoma, a number of pharmacodynamic studies have been conducted in transformed human tumour cell lines and in-vivo tumour models. These findings are not considered relevant for the purposes of the present application.

Conventional safety pharmacology tests for CNS effects in mice and cardio-respiratory effects in conscious dogs were negative. The potential of alitretinoin for QT-prolongation was examined in vitro in a whole cell patch clamp assay using HEK293 cells stably expressing the HERG potassium channel. Alitretinoin was tested at concentrations of 1, 3, 10 and 30 μM. The highest concentration was limited by solubility. The test system was validated with E-3401 (selective IKr blocker) as a positive control at a concentration of 100 nM. There was no effect on HERG-mediated current at 1 and 3 μM. Precipitation was observed at concentrations ≥30 μM. The maximum inhibition at 30 μM was 26.42%, and no IC_{50} could be determined. Although an IC_{50} value could not be determined because of the poor solubility of the test compound, the test was clearly negative at a concentration of unbound alitretinoin equal to 3 μM. This corresponds to a safety margin relative to the C_{max} of unbound drug in patients of about 500. As such, further in-vitro testing for QT prolongation is not warranted.

III.2 Pharmacokinetics

Alitretinoin and its metabolites were analysed by validated HPLC-UV methods. The quantification limit for alitretinoin was 1-10 ng/mL.

Non-clinical PK data are limited, but generally consistent with those reported for other RAs. After IV administration to rats, dogs and cynomolgus monkeys, the mean elimination half-life were 0.6 h, 1.5 h, and 0.9 h, respectively. Clearance amounted to 25.4, 4.9, and 7.6 mL/min/kg, respectively, representing approximately 40%, 10%, and 30% of the hepatic blood flow in the three species. The volume of distribution was 0.87 L/kg in rats, 0.30 L/kg in dogs, and 0.45 L/kg in monkeys. After oral administration to rats (40 mg/kg), dogs (20 mg/kg), and monkeys (20 mg/kg), alitretinoin was rapidly absorbed with a mean t_{max} of 0.25 h, 1.0 h, and 2.0 h, respectively. Mean oral bioavailability in the rat, dog, and cynomolgus monkey amounted to 5%, 44%, and 16%, respectively. In long-term toxicokinetic studies in the rat and dog, the kinetics of alitretinoin was roughly linear with dose and time, with no relevant sex differences. However, in 8-week and 13-week studies in mice as well as in a 4-week study in dogs, exposures to alitretinoin tended to become sub-proportional with time.

In a quantitative whole-body autoradiography study in male rats receiving single and repeated doses of ^{14}C-labeled tretinoin, the gastrointestinal tract was the organ most markedly exposed to drug-related material, followed by the liver. Radioactivity was widely distributed to other tissues and organs, including the skin, and was similar after single and multiple oral doses. No study was conducted with alitretinoin, but according to the Applicant whole-body distribution of the two compounds would be expected to be similar since alitretinoin is an isomer of tretinoin exhibiting similar pharmacokinetic properties. This is accepted.

Plasma protein binding was 96.7%, 97.1%, and 94.9% in the mouse, rat, and dog, respectively, versus 99% in humans.

In rats and dogs, oral alitretinoin was metabolised predominantly by oxidation via CYP3A4. The metabolic profile in animals in vivo was similar to that in humans, with the 4-oxo-metabolite of alitretinoin constituting the major metabolite in all species. In in-vitro studies with isolated recombinant human CYP450, alitretinoin competed only with CYP3A4 but not with CYP1A2, 2C1, 2C9, and 2D6. The concentration of alitretinoin achieving 50% inhibition (IC_{50}) of CYP3A4 was 1350 ng/mL (unbound), about 10 times higher than the maximum average C_{max} of 150 ng/mL in patients administered 30 mg /day for up to 12 weeks (Protocol No. BAP00200). In vivo-induction of CYP450 isozymes was observed in rat liver during a 13-week oral toxicity study in rats. In humans, however, dose proportionality was confirmed in patients treated with 10 mg or 30 mg oral alitretinoin once daily up to 24 weeks CHE (BAP00200).

Non-clinical PK interaction studies were limited to a hexobarbital sleeping time and zoxazolamine paralysis study in mice and to a series of in-vitro studies of the effect of alitretinoin on the metabolism on the sex hormones medroxyprogesterone, progesterone, norgestimate and norethindrone. There were no biologically significant findings in these studies at clinically relevant doses or concentrations. Interaction studies with oral contraceptives, ketoconazol, ciclosporin and simvastatin have been conducted in humans and are summarised in section 4.5 of the SPC.

III.3 Toxicology

The LD_{50} of alitretinoin was 1400 mg/kg in mice (IP) and 3000 mg/kg in rats (PO).

The pivotal repeat-dose studies were conducted in rats (26 weeks) and dogs (39 weeks). Toxicity findings were consistent with hypervitaminosis A. In rats, findings included impaired general condition, transient minor behavioural changes, minor changes in haematological and clinical chemistry parameters (e.g. reduced RBC parameters, increased platelet count and increased triglycerides), hypertrophy, glycogen storage and fatty change of the liver, bone fractures, thickening of epiphyseal cartilage, hyperplasia and hyperkeratosis of the fore stomach and oesophagus, degenerative changes in the female reproductive organs and eyes, and medullar calcification of the kidneys. In dogs, impaired general condition, skin and mucus membrane effects, gastro-intestinal irritation, minor changes in haematological and clinical chemistry parameters, liver hypertrophy and

degenerative and atrophic changes in the male reproductive organs were observed. The NOAELs were 0.67 mg/kg/rat in the rat and 0.7 mg/kg/day in the dog. In two sub acute toxicity studies were conducted in mice as preliminaries to the mouse carcinogenicity study, the NOAEL was 10 mg/kg/day based on testis lesions comprising reduced organ weight, vacuolisation of Sertoli cells and tubular degeneration.

In the rat study, alitretinoin was not measurable at all time points in the mid- and low-dose groups. In the high-dose group (6 mg/kg/day), the AUC at the end of the study was 157 ng.h/mL in females and 50.6 ng.h/mL in males. Assuming dose-linearity, this would correspond to AUC levels of 17.5 ng.h/mL in females and 5.65 ng.h/mL at the NOAEL (0.67 mg/kg/day). In the dog study, the AUC at the NOAEL (0.7 mg/kg/day) was 268 ng.h/mL in females and 172 ng.h/mL in males. In the sub acute mouse studies, the AUC in male mice at the NOAEL based on testis lesions (10 mg/kg/day) was 221 ng.h/mL. In patients administered alitretinoin 30 mg/day for up to 12 weeks (Protocol No. BAP00200), the maximum average AUC recorded was 363 ng.h/mL. Thus, AUC-based safety margins are well below 1, which is hardly surprising given the well-known toxicities of vitamin A and its RA metabolites.

Alitretinoin was tested for genotoxicity in a conventional battery of GLP-compliant in-vitro and in-vivo assays. Although findings in the human lymphocyte test were equivocal at short-term incubation in the absence of S9 mix, the weight of evidence indicates that alitretinoin is not genotoxic.

Conventional carcinogenicity studies were conducted in mice and rats. Neoplastic lesions were limited to a borderline (M: 1/50, F: 3/50; historical background: 2%) increase in osteosarcoma in mice at 10 mg/kg/day. As bone atrophy and fibrous osteodystrophy were common at dose levels above 3 mg/kg/day and there were no tumours in the high dose group (30 mg/kg/day), the marginally increased incidence in osteosarcomas in the mid-dose group is considered secondary to the dystrophic lesions of the bone and as such has little immediate relevance to humans.

Due to the known teratogenic potential of retinoids, reproductive toxicity studies with alitretinoin only included an in-vitro exploratory assessment of teratogenic, an exploratory embryotoxicity/teratogenicity study in mated mice, and a regulatory Segment I study of fertility and early embryonic development to implantation in rats.

In repeat-dose studies in dogs (39 weeks) and mice (13 weeks), exposure to alitretinoin was associated with atrophic and degenerative lesions in the male sexual organs. This is reflected in sections 4.6 and 5.3 of the SPC.

In the Segment I study, the NOAEL for male and female fertility was 10 mg/kg/day, the highest dose-level tested. Although some plasma samples were analysed for alitretinoin to confirm adequate exposure, AUC levels are not available for this study. In a separate 4-week oral gavage TK study in rats, however, AUC levels at the end of the study were 358 ng.h/mL in females and 279 ng.h/mL in males, that is, lower than the maximum average AUC of 363 ng.h/mL in patients administered alitretinoin 30 mg/day for up to 12 weeks (Protocol No. BAP00200). Therefore, no conclusions can be drawn from this study in respect of the potential of alitretinoin to impair fertility in humans. As such, a potential risk to male fertility cannot be excluded, as will be mentioned in sections 4.6 and 5.3 of the SPC.

Tests for embryo-foetal toxicity included two non-GLP exploratory studies. In an in-vitro assay for teratogenic activity, the IC_{50} for alitretinoin was 100 nM. The corresponding values for isotretinoin and tretinoin were 70 nM and 80 nM, respectively. As such, alitretinoin was concluded to have a teratogenic potential similar to that of isotretinoin and tretinoin. In the in-vivo study, alitretinoin was administered orally by gavage (in raps-seed oil) to mated mice at doses of 0, 10, 55, or 300 mg/kg/day on Days 8 and 9 of gestation. The number of foetuses was reduced, and foetal resorption rate increased at 55 mg/kg and 300 mg/kg. The number of abnormal foetuses (mainly cleft palate, ear malformations, and tail malformations) indicated a clear teratogenic effect at 55 mg/kg. Total foetal resorption occurred at 300 mg/kg. Such effects were not observed at 10 mg/kg/day. In conclusion, alitretinoin was teratogenic at 55 mg/kg/day and embryolethal at 300 mg/kg/day. Since alitretinoin was found to

be equally teratogenic to isotretinoin and tretinoin, Toctino is contraindicated in pregnant women and in women of childbearing potential that do not meet all the conditions of a strict pregnancy prevention program. Therefore, no regulatory, GLP-compliant Segment II or Segment III studies were performed. This is accepted.

No studies were conducted in juvenile animals as Toctino is indicated for adults only.

There are no impurities in the drug substance or drug product that require qualification.

Alitretinoin absorbs light within the UVA range and, like other retinoids, was confirmed to be phototoxic in conventional in-vitro and in-vivo models. Due warnings are included in the SPC.

III.4 Ecotoxicity/environmental risk assessment

The Applicant has submitted an Environmental Risk Assessment which includes all phases, tiers and compartments stipulated in the applicable CHMP guideline. The outcome of this exercise indicates that alitretinoin does not represent a risk to the aquatic environment, including ground water, and is unlikely to lead to significant bioaccumulation in fish. The risk ratios for sediment and soil cannot be calculated, however, as there are no experimental data on the effects of alitretinoin on sediment and soil dwelling organisms.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Results of Relative Bioavailability / Bioequivalence Studies

Study BAP00066 demonstrated that the relative bioavailability of alitretinoin was similar for the Phase 3 20 mg capsule (code D) and the Phase 2 20 mg capsule (code B). Plasma levels of alitretinoin metabolites were also similar between the two formulations. Study BAP00300 demonstrated that the proposed commercial formulation and the Phase 3 formulation were bioequivalent. AUClast and Cmax for alitretinoin and the main metabolite (4-oxo alitretinoin) were within the defined bioequivalence range, except that the lower confidence limit for Cmax at the 10 mg dose (79.5%) was just outside the bioequivalence range. This finding is however not considered to be clinically relevant since bioequivalence was confirmed for AUClast. Bioequivalence was also demonstrated for the principal metabolite of alitretinoin, the 4-oxo-metabolite, following administration of either 10 mg or 30 mg doses.

By far the biggest impact on bioavailability was the intake of food which increases exposure to alitretinoin by a factor of 4. Accordingly in all clinical studies patients were advised to take alitretinoin with a meal and the same recommendation is included in the proposed SPC.

A total of 447 subjects have been enrolled in 9 clinical pharmacology studies (364 subjects), or in 2 therapeutic studies (82 patients in BAP00003 and BAP00200) in which pharmacokinetic parameters or drug exposure were measured. Of these, 234 have received single doses of alitretinoin from 5 to 150 mg (including subjects given repeated single doses in crossover design studies, with washout periods between each dose), and 213 have received multiple once-daily doses of alitretinoin ranging from 5 mg to 40 mg, with total treatment duration up to approximately 6 months.

Dose proportionality

Oral administration of alitretinoin once daily at doses of 5, 10, and 20 mg for 14 days led to dose proportional drug exposure on Days 1 and 14. Dosing with 20 mg resulted in a moderate (24%) decrease in alitretinoin exposure on Day 14, compared to Day 1. Dosing with 5 mg or 10 mg led to similar alitretinoin exposure on Days 1 and 14.

The pharmacokinetic parameters of alitretinoin and the main metabolite 4-oxo-alitretinoin (BAL8078) were in good agreement with those determined in previous studies.

Time dependency
Results of studies BAP00012 and BAP00117 in healthy volunteers indicated a dose-dependent time effect on drug exposure following once-daily oral administration. When given at low doses (5 mg or 10 mg), AUC and Cmax values of alitretinoin and 4- oxo-alitretinoin were similar on dosing days 1 and 14, but at higher doses (20 mg or 40 mg) exposure was lower on day 14 than on day 1, with the decrease in exposure more pronounced for the 40 mg dose. In contrast, results of study BAP00200, carried out in patients with moderate or severe CHE and results of BAP00134 carried out in healthy volunteers did not show a time effect of exposure after chronic administration for up to 24 weeks.

Distribution
In healthy volunteers and patients, the dominant half-life for alitretinoin ranged from 2 to 10 hours. The plasma protein binding of alitretinoin in humans was 99.0%. There was no indication of any gender difference in humans with mean protein binding values of 99.0% in males and 99.1% in females. Based on these results, extensive clinical studies of plasma protein binding were not performed. As shown in the table below, the mean volume of distribution of alitretinoin varied from 259 L to 1071 L. The large variability (> 50%) of the volume of distribution presumably reflects more the variability in absorption (Cmax and AUC) than in distribution. The volume of distribution of alitretinoin was greater than total body water, in agreement with the known distribution of endogenous alitretinoin in tissues. The volume of distribution was not dose-related. Results of study BAP00200 demonstrated that there was no major difference in the distribution/bioavailability between males and females and between healthy volunteers and patients.

Metabolism
As for other endogenous retinoids, oxidation and isomerization are the main metabolic pathways for alitretinoin. In all clinical pharmacology trials, the main metabolite of alitretinoin in plasma, increasing in a dose-proportional fashion, was 4-oxo-alitretinoin, and this was also the finding in animals. The 4-oxo-metabolite was the major metabolite in plasma in healthy volunteers and patients, both male and female. Other isomers contributed to the overall drug exposure but their concentrations were independent of the alitretinoin dose.
In the mass balance study BAP00035, no unchanged drug was found in urine, and the most abundant identifiable excretion product in humans (6.5% of the dose in urine) was a glucuronidated form of 4-oxo-alitretinoin. The occurrence of a glucuronide conjugate indicates involvement of phase II metabolism.
Based partly on data from the mass balance study BAP00035, the metabolism for alitretinoin appears to proceed in a way similar to that of its structural isomer vitamin A, with formation of glucuronide conjugates and the C9 side chain cleaved in sequential steps into shortened products, such that metabolic products comprise a variety of smaller molecules, each at concentrations too low for individual identification. In all multiple-dose clinical pharmacology studies the extent of metabolism was variable but independent of the dose and the gender.

Elimination
Metabolism is the main elimination pathway of oral alitretinoin. Results of the mass balance study BAP00035 demonstrate that oral alitretinoin is absorbed, extensively metabolized, and quantitatively eliminated. Elimination of alitretinoin and its major identified metabolite 4-oxo-alitretinoin occurs rapidly, with elimination half-life of approximately 2 to 10 hours. Elimination of all drug-related material is complete within 11 days after administration. Excretion is mainly in urine (63%) with a smaller amount in faeces (30%) with mean total excretion amounting to 93.5% of the administered dose.

Essentially no unchanged drug can be detected in urine or faeces, and excretion products comprise the glucuronide of 4-oxo-alitretinoin (6%) and numerous small molecular entities, most of which are present in amounts too low to identify.

Pharmacokinetics in Special Populations
Pharmacokinetics of alitretinoin has not been studied in subjects with impaired renal or hepatic function. As for other oral retinoids, the use of oral alitretinoin in patients with severe renal or hepatic insufficiency is contraindicated because of the lack of these investigations. Paediatric populations have

not been studied because CHE does not occur in children. Pharmacokinetic in elderly subjects was not specifically investigated. No relevant differences in pharmacokinetic were found between men and women.

IV.2 Pharmacodynamics

Chronic hand eczema is characterized by a mixture of inflammation and hyperkeratosis. The exact mechanism of action of alitretinoin in patients with chronic hand eczema is not known. However, alitretinoin has both anti-inflammatory activity (suppresses production of chemokines, recruitment of peucocytes and inhibits T-lymfocyt function in inflamed skin).

In addition alitretinoin, as other retinoids, may normalize the dyskeratosis/hyperkeratosis seen in the epidermis of patients with chronic eczema. The applicant states that it has not been possible to identify reliable pharmacodynamic surrogate markers for clinical effect. However, a clear relationship between dosing, efficacy and increasing levels of clinical adverse effects has been demonstrated.

No relationship between plasma exposure, efficacy, and side effect has been demonstrated.

IV.3 Clinical efficacy

The clinical efficacy of alitretinoin in patients with chronic hand eczema is based on data from a total of 5 clinical trials, 2 phase-III pivotal trials (BAP00089 and BAP00091), a phase-II dose-response study (BAP00003), a combined pharmacokinetic and clinical study (BAP00200) and an open-label long-term safety study (BAP0626). An overview of the efficacy studies is shown in the table below.

Protocol Number and Study Title	**Obejctives**	**Study Design**	**Dose regimen and treatment duration**	**Number of Patients** **Disease severity**
BAP00089: Efficacy and Safety of alitretinoin in the Treatment of Severe Chronic Hand Dermatitis	To demonstrate that the response rate based on Phydician Global Assessment (PGA) in one or both active treatment groups is superior to the response rate in the placebo group at the end of therapy. To assess the safety of tested dose regimens. To determine time to relapse To demonstrate the efficacy based on secondary efficacy parameters.	Double-blind, randomized, placebo-controlled, parallel-group, multicentre.	10 mg or 30 mg or placebo, QD 2:2:1 randomization 12-24 weeks	1032 patients Severe CHE
BAP:00091: Follow-up Efficacy and Safety Study of alitretinoin in the Treatment of Chronic Hand Dermatitis Refractory to Topical Therapy.	To assess the safety and efficacy of a 12-24 week course of alitretinoin in patients with chronic hand dermatitis refractory to topical therapy, who were previously treated in study BAP00089 with alitretinoin or placebo.	Double-blind, randomized, placebo-controlled, parallel-group, multicentre.	10 mg or 30 mg or placebo, QD 12-24 weeks	352 patients Relapsed severe CHE
BAP00003: Efficay and Safety Study of Alitretinoin in the Treatment of Chronic Hand Dermatitis.	To assess the safety and efficacy of alitretinoin, at 10 mg, 20 mg, or 40 mg QD in patients with moderate and severe chronic hand dermatitis refractory to topical treatment.	Double-blind, randomized, placebo-controlled, parallel-group, multicentre study.	10 mg, 20 mg, 40 mg or placebo, QD 12 weeks	319 patients Moderate to severe CHE
BAP00200:	To assess pharmacokinetics,	Double-blind,	10 mg or 30 mg,	32 patients

Pharmacokinetics, efficacy and safety of alitretinoin in patients with severe or moderate chronic hand dermatitis refractory to topical therapy.	efficacy and safety of alitretinoin during multiple oral dosing of 10 or 30 mg QD for 12 or 24 weeks, in patients with severe or moderate refractory CHE.	randomized, placebo-controlled, parallel-group, single centre	QD 12-24 weeks	 Moderate or severe CHE
BAP0626: Efficacy and Safety of Alitretinoin in the Treatment of Severe Refractory Chronic Hand Dermatitis.	To assess the safety and efficacy of alitretinoin. To demonstrate the efficacy of alitretinoin in patients with severe refractory CHE, based on PGA and other secondary efficacy parameters. To assess patients reported outcome.	Multi-dose, open-label, multiple centre study	30 mg QD 24 weeks	252 patients Severe CHE

IV.4 Clinical safety

The safety database comprises all subjects and patients who received at least one dose of alitretinoin or placebo in the sponsored studies. A total of 363 healthy individuals and 1630 patients with hand eczema recruited in the pharmacological and therapeutic studies are included in the safety database. An overview of the number of patients exposed to alitretinoin in the most important studies and the duration of therapy is shown below.

Pooled Analysis (N)	Studies Included	Patients treated with 30 mg alitretinoin	Patients treated with 10 mg alitretinoin
All patient studies (N = 1630)	BAP00089 BAP00003 BAP00200 BAP00626	674 (221 for 24 weeks)	514 (240 for 24 weeks)
Blinded patient studies (N = 1382)	BAP00089 BAP00003 BAP00200	426 (182 for 24 weeks)	514 (240 for 24 weeks)
Extended treatment study (N = 1031)	BAP00089 BAP00091	410 (181 for 24 weeks; 58 for 48 weeks)	418 (239 for 24 weeks; 7 for 48 weeks)
Healthy volunteer studies (N = 129)	BAP00012 BAP00033 BAP00117 BAP00134	54	12

In the phase-II and III studies routine safety endpoints, including liver and thyroid function and lipid-profile, were collected and in addition subgroups of patients were examined for systemic retinoid toxicity including skeletal radiography (with focus on extra osseous calcification and hyperostosis), bone mineral density scans, ophthalmology (conjunctivitis and keratitis) and psychiatric tests (with focus on depression).

In summary alitretinoin therapy was not associated with extra osseous calcifications, hyperosteosis, osteoporosis or depression. The typical class adverse effects of oral retinoids were seen during treatment with alitretinoin such as mucocutaneous dryness, headache, flushing, increase in serum concentrations of cholesterol, triglycerides and creatinine phosphokinase and decreased serum concentrations of haemoglobin, TSH and free T4. Abnormal liver function test was not observed in alitretinoin treated patients.

Based on collected data in the placebo-controlled studies the most frequent adverse drug reactions associated with alitretinoin therapy were: headache (30 mg: 21%, 10 mg: 11%), flushing (30 mg: 5.9%,
10 mg:1,6%), increased levels of triglycerides (30 mg: 35,4%, 10 mg: 17%), increased levels of 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

adverse events were dose-dependent and all reversible. The adverse event profile of alitretinoin in the long-term study and during re-treatment was similar to that observed during the placebo-controlled phase.

Serious adverse events
One pregnancy occurred during clinical trials in a patient who failed to comply with defined contraceptive measures. The pregnancy was terminated. One patient developed signs compatible with pseudotumor cerebri.

IV.5 Discussion on the clinical aspects

Efficacy
The Applicant has shown that treatment with alitretinoin 30 mg once daily and to a lesser extent alitretinoin 10 mg once daily, for up to 24 weeks may induce remission in patients with severe corticosteroid-refractory hand eczema. In addition patients who experience a relapse of the disease re-treatment with alitretinoin for up to 24 weeks may similarly reduce the signs and symptoms of the hand eczema. Patients with recurrent chronic palmar vesicular eczema (pompholyx) are less likely to respond to therapy in contrast to those with predominant hyperkeratotic scaly lesions.

Safety
In general the safety-profile of alitretinoin in patients with severe chronic hand eczema is expected for an oral retinoid. Alitretinoin is teratogenic, as other retinoids.

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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The Benefit-Risk assessment of the Reference Member State and the Concerned Member States reached consensus with a positive outcome at Day 191 of the procedure, July 30, 2008.

It was concluded that the legal status Toctino is subject to prescription which may not be renewed.

Furthermore, the following follow-up measures were agreed:

- The first 3 production scale batches of the active substance will be put on stability and tested according to the stability protocol as presented in section S.7.1.

- The enclosed stability studies will be continued.

- The validation campaign for Toctino is planned for the 4th quarter of 2007. From this campaign, at least 3 batches of each strength will be placed on stability under real time and accelerated conditions according to ICH guideline Q1A(R2). The protocol is presented for this planned stability program with test parameters and procedures similar to those used in the studies already performed.

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

VI. MODULE ON UPDATES

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)