SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Panretin. This scientific discussion has been updated until 30 June 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Panretin gel contains a new active substance (INN alitretinoin, 0.1% w/w) developed by Ligand Pharmaceuticals UK Limited. The approved indication for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (KS) when:

- lesions are not ulcerated or lymphoedematous, and
- treatment of visceral KS is not required, and
- lesions are not responding to systemic antiretroviral therapy, and
- radiotherapy or chemotherapy are not appropriate

and is subject to restricted medical prescription. Panretin gel is initially applied two times a day to cutaneous Kaposi's sarcoma lesions and the application frequency can be increased stepwise to three or four times a day according to individual lesion tolerance, allowing no less than two weeks between application frequency increases. Similarly, the frequency of application can be reduced if application site toxicity occurs (see SPC section 4.2, *Posology and method of administration*).

Retinoids

The compounds of the vitamin A family of molecules are commonly referred to as retinoids. These include retinol and closely related naturally occurring molecules as well as synthetic analogues.

The retinoic acids (RAs) are similar to the retinols except for oxidation of the -OH group. While these molecules may not have the effects of the retinols on the eye and on reproduction, RAs strongly promote growth and differentiation of epithelial tissues in vitamin-A-deficient animals; all-*trans*-retinoic acid (ATRA) has 10 to 100-fold the activity of retinol in this regard. Among the synthetic analogues, aromatisation of the β-ionone ring gave rise to etretinate, from which acitretin is produced *in vivo*; the latter has now replaced etretinate in therapeutic use.

RAs influence gene expression by binding to specific nuclear receptors, which have been grouped into two families. ATRA binds preferentially to RAR receptors (α, β, γ) with much less affinity for RXR receptors. In contrast, 9-*cis*-RA (alitretinoin) is not only able to bind to RAR but is also an endogenous RXR ligand. Among certain genes regulated by hormones, activation involves binding of the hormone-receptor complex and then dimerisation with an RXR-ligand complex. In this way, retinoids can influence the expression of receptors and influence cell growth.

The ultimate effect of retinoids on epithelia is to inhibit hyperplasia and to promote cell differentiation. A slowing in chemical or viral-induced progression of pre-malignant to malignant cells has been shown in animals, although effects on established tumours are generally limited. The mechanisms by which vitamin A and its derivatives may have an antitumour effect are still not entirely clear. In addition to the effects on promoting cell differentiation, there are effects on the immune system (cell-mediated and humoral immunity). Vitamin A deficiency has also been associated with increased susceptibility to bacterial, parasitic and viral infections.

Kaposi's sarcoma

Kaposi's sarcoma (KS) was first described as an indolent tumour seen in equatorial Africa and, to a much lesser extent, in Mediterranean countries. With the advent of AIDS, KS was noted to be the commonest neoplasm seen in HIV-infected patients and was found to be particularly common among homosexual patients, with 20-30% affected at some time. Moreover, KS appeared to be much more aggressive in these individuals. The appearance of cutaneous and/or visceral lesions is sometimes the first clue to HIV infection and KS may present even when the CD_4 count is preserved, although exacerbations are seen in association with drops in lymphocyte counts and during intercurrent

opportunistic infections. KS lesions may be very noticeable especially when there is also associated blocking of regional lymphatics; visceral KS involvement can be rapidly fatal.

The suspicion that KS is the manifestation of a viral infection was supported by the cloning of novel herpes-like sequences from biopsies and the identification of the genome of a γ-herpes virus, now called HHV-8 (or KSHV), in both AIDS-related and non-AIDS-related KS. A correlation has been shown between the HHV-8 DNA load in KS lesions and the severity and staging of the disease. HHV-8 also appears to be latent in body-cavity-based lymphomas in AIDS patients, where it is detected alone or in association with other γ-herpes viruses such as Epstein-Barr virus.

Management of KS depends on the extent of cutaneous/visceral involvement and the level of immunosuppression; curbing the HIV viral load and increasing the CD_4 count may provide some amelioration or even halt progression of KS. Local lesions, when few in number, may be excised or treated with cryotherapy or radiotherapy; intra-lesional injection of vinblastine may also be effective. Interferon-α is used for patients with non-life-threatening KS when the CD_4 count is >200 and the viral load is low. Once there is evidence of widespread cutaneous and/or systemic disease, systemic chemotherapy is needed.

2. Chemical, pharmaceutical and biological aspects

Composition

Panretin gel contains the new active substance, alitretinoin, which is 9-*cis*-RA. The finished medicinal product is presented as a topical gel, based on formulations, which have been used for other retinoids, with strength of 0.1% w/w. The excipients used are standard ingredients for a topical product of this type. The product (60 g) is contained in an epoxy-lined collapsible aluminium tube with a white high-density polyethylene cap.

Active substance

Alitretinoin is 9-*cis*-RA or (2*E*, 4*E*, 6*Z*, 8*E*)-3,7-dimethyl-9- (2,6,6-trimethyl-l-cyclohexenyl)-2,4,6,8-nonatetraenoic acid according to IUPAC nomenclature. Alitretinoin contains no chiral centres but a variety of geometrical isomers are possible. Satisfactory proof of structure has been demonstrated by a number of spectroscopic techniques, particularly NMR.

Alitretinoin is manufactured using a synthetic process, which is stereospecific for the geometry at positions 4, 6 and 8 and stereoselective for position 2. The data submitted indicate that alitretinoin is manufactured by a method, which can provide reproducibly pure batches of active substance, especially with regard to isomeric composition. Details are provided of the use of batches in toxicological, clinical and other studies. Clinical trial material has been produced at two sites of manufacture using slightly different routes of synthesis. Data have been presented to demonstrate that material produced using either route of synthesis is chemically equivalent: the only likely additional impurity arising from the commercial process has not been detected in batches of active substance.

A validated HPLC method is used for both the assay and control of related substances. The assay limits are adequate. Toxicological data confirm that the proposed related substance specifications for alitretinoin are reasonable.

Details are provided from various sites relating to four laboratory scale batches and 10 large scale batches and were in compliance with the existing specifications. The data for the full-scale batches show that the manufacture of the active substance is reproducible and that the material is acceptably pure. Solvents have been present only at low levels, usually below the quantitation limit of the method employed. Heavy metals have been present at less than 20 ppm in all batches of alitretinoin.

Stress stability studies were conducted on the active substance stored at 60ºC as suspensions in water and aqueous 0.1N HCl and in solution in ethanol and aqueous 0.1N NaOH. Additional samples were stored with oxygen in the headspace of the container. The ethanolic solutions were also exposed to fluorescent and UV light, at 10,100 lux and 1.7 W/m^2 respectively. Decomposition was extensive in the presence of oxygen, as expected, giving rise to a large number of impurities.

The proposed re-test period of 12 months, after storage in the dark at –76ºC in amber glass bottles with argon filled head-space, is justified by the long-term and accelerated stability data provided.

A photostability study was conducted on one batch at ambient temperature in accordance with the current ICH guideline (total illumination 1.2M lux hours) and showed that degradation of alitretinoin was accelerated by exposure to light, hence the need to protect the active substance from light.

Other ingredients

In addition to the active substance, the gel contains dehydrated alcohol (ethanol) as the principal vehicle (solvent) with polyethylene glycol 400 and hydroxypropyl cellulose providing cosmetic acceptability and thickening of the alcoholic solution. Butylhydroxytoluene (BHT) at 0.05% w/w is the chosen antioxidant. The excipients meet the requirements of their appropriate monographs (Ph. Eur. for BHT, polyethylene glycol 400 and hydroxypropylcellulose). Dehydrated alcohol is of BP quality and the nitrogen gas used to fill the headspace, complies with Ph. Eur. monographs. Satisfactory certificates of analysis are presented. Assurance has been provided that the alcohol used in the finished product will comply with the Ph. Eur. monograph, which came into force in January 1999, in particular with the limit of 2 ppm for benzene. The quality specifications and tests relating to the packaging material (aluminium tubes, epoxy-lined) are satisfactory.

Product development and finished product

Manufacturing process

The product is a topical gel based on formulations that have been used for other retinoids. The active substance is dissolved in alcohol and the gel is thickened with hydroxypropylcellulose. Butylated hydroxytoluene is added as an antioxidant. The gel is self-preserving and is packed in epoxy-lined collapsible aluminium tubes.

Specifications

Concerning the test specification of the product, assay limits were in compliance with EU Directives.

The method to control viscosity and the viscosity limits chosen to reflect batch analysis data at release and end of shelf life are considered justified.

GMP

Durham Pharmacal, a subsidiary of Stiefel, manufactures the product in the USA. The product is being manufactured in a facility that holds the necessary Manufacturing Authorisation (see Annex II of the Opinion).

Stability of the product

The stability data support the proposed shelf life of 24 months. In-use stability studies have been conducted which justify the proposed shelf life after opening of 90 days. In addition, the content of ethanol in the gel is considered to provide adequate microbial protection.

Discussion on chemical, pharmaceutical and biological aspects

The information in the dossier is well presented with full explanations of the development of the active substance and finished product together with detailed histories of the analytical development.

The data submitted indicate that pure, large-scale batches of alitretinoin can be manufactured reproducibly. The degradation of RAs is complicated and may give rise to a large number of potential impurities. Satisfactory evidence, however, has been provided to show that the quality of the active substance is maintained by the proposed storage conditions. The limits for related substances and residual solvents in the active substance specification are acceptable. The formulation of the gel is based on alcohol thickened with hydroxypropylcellulose and its manufacture is reproducible.

The proposed in-use shelf life of 90 days is supported by the stability data and limits for assay, degradation products and viscosity are satisfactory to ensure the reproducible clinical performance of the product.

3. Toxico-pharmacological aspects

Introduction

The Applicant has mostly focused on ascertaining the activity of Panretin *in vitro* and safety in animals in order to proceed to the clinical stage of development. Preclinical studies were conducted to GLP guidelines. Many of the pharmacokinetic and toxicity studies using oral administration with subsequent systemic exposure are not of primary relevance due to the observation that systemic exposure following topical administration in clinical use does not occur (see also Part IV, Clinical Aspects).

Pharmacodynamics

The effect of alitretinoin on KS cells *in vitro* seemed to be predominantly anti-proliferative. In experiments conducted both *in vitro* and *in vivo* it was shown that alitretinoin binds to and activates all intracellular retinoid receptor subtypes (RAR and RXR). Alitretinoin is likely to have a different mechanism of action from 13-cis-RA and ATRA although there are no data regarding the possible molecular mechanisms of alitretinoin's anti-proliferative action in KS cells. There is bibliographical evidence for the involvement of both RAR and RXR-dependent signalling pathways in the induction of tissue transglutaminase and apoptosis in a human myeloma cell line. However, alitretinoin did not appear to be cytotoxic or apoptogenic on KS cells *in vitro*. A study of the effects of alitretinoin and ATRA on thymidine uptake by cultured KS cells did not provide insight into any properties specific to alitretinoin. At the time of development, adequate animal models of KS in which to test 9-cis-RA were lacking. With respect to inhibition of DNA synthesis, the value of simultaneous activation of RXR and RAR by alitretinoin compared to simple activation of RAR remains to be determined.

Interaction with cisplatin resulting in enhanced antitumour efficacy was shown. Safety pharmacology did not demonstrate any effects of clinical significance on the CNS and cardiovascular system. Effects on the respiratory system were not investigated.

Pharmacokinetics

Pharmacokinetic studies following administration by the dermal, oral and i.v. routes were conducted in rats, dogs and/or rabbits. Safety margins that were 1-3 orders of magnitude greater than human plasma concentrations were established. The highest tissue concentrations after oral administration were found in liver, adrenal glands, fat, kidneys, mesenteric lymph node, lung, skin and ovaries. After oral administration there was no evidence of accumulation and the primary route of excretion was faecal.

Systemic exposure to alitretinoin was measurable in both male and female rats following topical application of a 0.5% alcoholic gel at a volume of 0.25 ml (*i.e.*, 1.25 mg alitretinoin) to shave dorsal skin. Alitretinoin was slowly and irregularly absorbed, as indicated by the t_{max}, which on day 1 averaged 24 h in females (n=2) but ranged from 6 to 24 h in males (n=6). Mean plasma concentrations, in terms of C_{max} and AUC, were higher in males than females, but the reason remains unclear. Both sexes showed time-dependent accumulation of alitretinoin and its 9,13-di-*cis* isomer over the five-day test period. Consistent with this accumulation, faecal and urinary excretion of radioactivity increased throughout the study.

According to bibliographical data CYP1A1, CYP1A2, CYP2C9 and CYP3A4 are likely to be involved in oxidative metabolism of alitretinoin.

Toxicology

General toxicity studies of up to 3 months oral dosing were conducted in rats and dogs. Dogs were less sensitive to alitretinoin with only liver and kidney identified as target organs as well as canalicular bile stasis and lymphoid depletion. In rats liver, mesenteric lymph nodes, stomach, spleen, heart, bone and adrenals were target organs.

A 28-day dermal toxicity study in the rat exposed to an alcoholic gel formulation of alitretinoin with the same excipients as alitretinoin gel, ascorbic acid and butylated hydroxyanisole was performed. Alitretinoin was administered to rats at more than 80 and 40 times the total daily clinical application rate (0.5 ml/day and 0.25 ml/day of the 0.5% formulation) and about 8 times with the 0.05% formulation. The range of doses was wider than is usually applied in dermal toxicity studies (1 to 10

times the therapeutic application). The histopathological findings were confined to the skin of the application site.

In view of the negligible systemic exposure following clinical application of Panretin, fertility studies were not conducted and the reproduction toxicity programme consisted only of oral teratogenicity studies in rats and rabbits. In anticipation that these would only confirm the well-established teratogenicity of a retinoid, these were conducted with substantially fewer animals than normal. Alitretinoin was confirmed to be a teratogen, both in the rabbit and in the rat (see SPC, section 4.3 *Contraindications* and 5.3 *Preclinical safety data*). Abnormalities included craniofacial and limb malformations.

A full package of genotoxicity studies was conducted comprising Ames test, mammalian cell mutation, clastogenicity and micronucleus test. Suitably high doses were used in all studies. There was no indication of genotoxicity.

Carcinogenicity and local tolerance studies with the intended clinical formulation were not conducted except for a dermal irritancy study in guinea pigs, which however provides scant detail and was not performed to GLP standards. The lack of oncogenicity studies seems justified in view of the lack of evidence of mutagenic potential, the natural history of AIDS-KS and the fact that systemic exposure for Panretin gel is expected to be negligible. Similarly, the lack of local tolerance studies is justified in view of the existing clinical trial experience and the fact that local tolerance study in animals are unlikely to provide useful additional information.

Four separate assays of phototoxicity were undertaken. These comprised photohaemolysis/haemoglobin oxidation, photocytotoxicity, photoirritation and photobinding to human serum albumen. Suitable positive controls were included. Alitretinoin was found to absorb UV light in the range 300-380nm (λmax=340nm) and in general to be phototoxic, albeit at high doses. Patients are advised to avoid direct sunlight (see SPC section 4.4, *Special warnings and special precautions for use*).

The limits of potential impurities (see Part II: Chemical, pharmaceutical and biological aspects), were justified on the basis of data from dermal toxicity studies.

Discussion on toxico-pharmacological aspects

The effect of alitretinoin on KS cells *in vitro* seemed to be predominantly anti-proliferative. At the time that alitretinoin was in preclinical development, no adequate animal models for KS in which the action of alitretinoin could be tested were available. A better investigation of the mechanism of action of alitretinoin in KS cells would have been desirable. However, the Applicant has mainly focused on ascertaining the safety in animals, and the activity *in vitro* and *in vivo* in order to proceed to the clinical stage of development.

Some of the pre-clinical studies presented are derived from generalising data obtained with 13-*cis*-RA and ATRA in different tumours types. Such generalisations need to be interpreted with caution in view of the ability of alitretinoin to interact with the RXR as opposed to 13-*cis*-RA and ATRA.

One toxicity aspect that is of potential clinical relevance is the well-established teratogenicity of retinoids as confirmed by the data presented. Therefore, the use of Panretin is contraindicated in pregnancy and lactation and this is reflected in the SPC (see SPC section 4.3 *Contraindications* and 5.3 *Preclinical safety data*).

The phototoxicity potential of alitretinoin was assessed based on its chemical properties and data from a battery of *in vitro* tests. The results suggest that alitretinoin absorbs light in the UV range, is subject to photodegradation to other isomers (predominantly ATRA) and was shown to have a weak potential to be a photo-irritant. Patients are advised to avoid direct sunlight (see SPC section 4.4**,** *Special warnings and special precautions for use*).

4. Clinical aspects

Topical alitretinoin in AIDS-KS was evaluated in nine Phase I/II studies and two double blind and vehicle-controlled Phase III studies with open-label extension phases (Table 1). The total number of

patients on Panretin evaluable for efficacy and safety is 469. No patient was younger than 18 years; only two patients were older than 60 years of age.

Clinical pharmacology

Pharmacodynamics

Given the relatively recent pharmacological characterisation of 9-*cis* RA, clinical data in the oncological setting were not available. Thus the pharmacodynamic rationale underlying the topical use of alitretinoin in the treatment of superficial KS lesions is based on assumptions and extrapolations from other retinoids in several tumour types which should be interpreted with caution.

ATRA, 9-*cis*-RA and 13-*cis*-RA have pleiotropic biological and pharmacological action. The three retinoids have anti-proliferative, apoptogenic and cyto-differentiating properties. In various *in vitro* cellular models of leukaemia and carcinoma, ATRA and 9-*cis*-RA cause growth arrest, cyto-differentiation and cytotoxicity, often due to activation of apoptosis. The cyto-differentiating action of ATRA is believed to be responsible for the clinical remission observed in virtually all patients suffering from acute promyelocytic leukaemia (APL), a rare form of acute myelogenous leukaemia which shows a typical rearrangement of the gene coding for the nuclear RA receptor RAR□. In this disease, ATRA causes granulocytic maturation of the leukaemia promyelocyte, which subsequently undergoes terminal differentiation and apoptosis. 9-*cis*-RA has proved superior to ATRA in causing apoptosis of APL and other myeloid leukaemia cells. ATRA and 13-*cis*-RA, in conjunction with interferons, have shown promising clinical activity in the treatment of head and neck cancer and in the chemoprevention of the recurrence of pre-neoplastic lesions like oral leukoplakia. Relevant to the present application, KS patients have been reported to benefit from systemic treatment with ATRA. At present it is not known whether the clinical action of retinoids on head and neck cancer, leukoplakia and KS is predominantly due to the anti-proliferative, apoptogenic or cyto-differentiating action.

Pharmacokinetics

Six of the nine Phase I/II trials in HIV positive patients with KS provided data on the systemic availability of alitretinoin after topical application of 0.05% and 0.1% gels. The assay methodologies involved HPLC separation of metabolites and quantitation either by UV absorption or by mass spectrometry (MS). The UV-detection methods had lower limit of quantitation (LLQ) 2.5 ng/ml for 9-*cis*-RA and for an oxidative metabolite 4-oxo-9-*cis*-RA, and LLQ 10 ng/ml for ATRA. The MS-detection method allowed for a LLQ of alitretinoin at 0.25 ng/ml and of 4-oxo-9-*cis*-RA at 0.80 ng/ml.

Percutaneous absorption

During Phase I/II studies, which involved both escalations from 0.05 to 0.1% gels and from twice daily (BID) to four times daily (QID), single timepoint samples (483) were obtained every 2-4 weeks. The mean number of lesions treated was 6.6 (median 4/patient). The median number of lesions treated in study L1057T-22, which provided 153 samples from 22 patients using the MS detection method was 11.5 (range 4-64); 15 of these patients treated ≥ 10 lesions.

The UV methods failed to detect alitretinoin, ATRA, or 4-oxo-9-*cis*-RA in plasma samples from 72/94 male patients. The MS method detected quantifiable alitretinoin, but not 4-oxo-9-*cis*-RA, in 26/153 samples (17%) and in 10/22 patients at some timepoint. Six of the 15 who treated at least 10 lesions had quantifiable plasma alitretinoin (in 15 samples) with a maximum concentration of 0.638 ng/ml, *i.e.*, similar to those reported to represent endogenous exposure in human plasma. There was no clear relationship between detectable alitretinoin or actual plasma levels and either the number of lesions treated, the strength of the gel used or time since last application.

In Phase I/II trials, 13/115 (11%) of patients took concomitant vitamin A-containing supplements up to RDA. Pharmacokinetic data are limited to the less sensitive assay and to 44 samples from 11/13 patients. Alitretinoin was not detectable in plasma by this assay, suggesting that supplementation within RDA has no marked effect on plasma alitretinoin.

Absorption from oral administration

Samples from patients with advanced cancer treated with 5-230 mg/m^2/day alitretinoin by mouth gave quantifiable (UV-detection) plasma concentrations of alitretinoin at all dose levels (mainly in the range 10^2 ng/ml), but with considerable inter-patient variability. Multiple dose pharmacokinetics

suggested that there was some induction of clearance at the higher dose levels (≥140 mg/m^2/day); there was little or no accumulation. Among samples from psoriatic patients treated with 0.15-1.5 mg/kg/day, alitretinoin was detected in plasma (at > 0.25 ng/ml) in 13/45 (29%) pre-dose samples on day 0 (max 0.67 ng/ml). Pre-dose concentrations on days 28 and 56 increased with increasing dose, reaching a mean maximum of 4.6 ng/ml while 2 h post-dose samples showed dose-related increases in alitretinoin and 4-oxo-9-*cis*-RA.

Metabolism

Oral dosing studies showed that concentrations of ATRA were < 10% those of alitretinoin, suggesting that minimal isomerisation of alitretinoin to ATRA occurs *in vivo*. Also, 0 and 6 h ATRA levels were almost all below the LLQ, which indicated that there was rapid clearance. These studies also showed that there was minimal isomerisation of alitretinoin to other potential isomers. Application of the MS analytical method to psoriatic patient samples demonstrated that in-vivo conversion of alitretinoin to 4-oxo-9-*cis*-RA occurred and that the latter reached concentrations which were about 50% of alitretinoin levels.

Alitretinoin metabolism appears to occur *via* oxidation to the 4-hydroxy and 4-oxo metabolites, with some isomerisation and some glucuronidation of parent and certain metabolites. CYP 1A1, 1A2, 2C9 and 3A4 are involved in these oxidative metabolic processes. Pharmacokinetic data from 71 patients co-treated with inhibitors of cytochrome P450 isoenzymes in Phase I/II showed that plasma alitretinoin remained below 2.5 ng/ml. In patients who had received concomitant inhibitors of CYP isoenzymes, the highest plasma concentration was similar to background levels. It was concluded that the pharmacokinetics of alitretinoin would not be significantly affected by other therapies because plasma levels after topical administration are similar to endogenous concentrations.

Excretion

In a published study of healthy volunteers treated orally with 20 mg/day alitretinoin or 13-*cis*-RA for 28 days which used HPLC and in-vitro microsomal assays, a glucuronide of alitretinoin was present in most day 14 and day 28 urines (at up to 19 ng/ml) and was produced by in-vitro incubation of alitretinoin with β-glucuronidase. At least three other glucuronidated metabolites, including 9-*cis*-4-oxo-RA glucuronide, were present and at higher concentrations than alitretinoin glucuronide.

Discussion on clinical pharmacology

The data obtained from Phase I/II patients who applied topical alitretinoin supported a conclusion that systemic exposure during gel treatment to KS lesions is not different from background exposure, regardless of whether patients took concomitant vitamin A supplements within the RDA. Thus, despite the mode of metabolism of alitretinoin, there appeared to be minimal potential for drug interactions to occur in those with normal or abnormal hepatic function.

Any potential for other drugs to increase the plasma levels of alitretinoin seen in association with topical Panretin would not be expected to be of any clinical importance. It is possible that drugs that induce CYP isoenzymes might reduce circulating levels of alitretinoin; this would have theoretical implications for efficacy but not safety. Any attempt at an analysis of efficacy according to concomitant medications that induce cytochrome P450 activity would not be likely to be useful due to small numbers. Given the possibility that vitamin A may favourably affect efficacy, the theoretical possibility of a negative effect on efficacy in case of co-administration with inducers has been mentioned in the SPC (see SPC section 4.5, *Interaction with other medicinal products and other forms of interaction*).

Alitretinoin appears to have some capacity to autoinduce its own metabolism when high oral doses are given. However, since only background levels of alitretinoin are found in plasma, it does not appear likely that Panretin therapy could result in induction of metabolism of other drugs that are substrates for CYP450.

Clinical efficacy

Topical alitretinoin in HIV-positive patients with KS was evaluated in Phase I/II studies (these consisted of a similar protocols implemented at nine different US sites) and two double blind and vehicle-controlled Phase III studies (L1057T-31 and ALRT1057-503) with open-label extension phases (Table 1). These pivotal studies were performed to GCP standards.

The primary efficacy measure recorded was response according to modified AIDS Clinical Trials Group (ACTG) criteria for local therapy (Table 2). All responses had to be maintained for at least four weeks. The area of a lesion was defined as the product of the longest diameter and the longest diameter perpendicular to this diameter. The lesion height was classified according to a three-point scale: macular (flat), plaque (≤ 2 mm height), nodular (> 2 mm height). The duration of response was taken from the date of first documented response to the date of documented disease relapse or the date of last follow up for patients still in response.

Table 1. Panretin gel clinical trials in KS

Study Ref. No.	Intended Doses of Panretin Gel	Duration of Panretin Gel Treatment	No. of Patients Receiving Panretin Gel	Study Design
Phase I-II studies	0.05, 0.1% gel BID to QID	Median 14 weeks range 0.7-96.3 weeks	115	Randomisation of patients to alitretinoin gel 0.05 versus 0.1%. Untreated lesions within each patient used as a reference.
L1057T-31	0.1% TID to QID	Blinded 12 weeks Blinded and open median 112 days range 1-497 days	134 100 (cross-over from vehicle to gel)	Phase III multicentre, double blind, randomised, placebo-controlled, parallel group, 12-week initial blinded phase then open follow-up. Possibility of blind cross-over for patients with disease progression during the 12 week period.
ALRT1057-503	0.1% BID	Blinded 12 weeks	62	Phase III, multicentre, double-blind, randomised, placebo-controlled parallel group. Possibility of entering patients into study ALRT1057-504 if disease progression during the 12-week period.
ALRT1057-504	0.1% BID	36 weeks open follow-up	58 (previously on vehicle gel) and 41/62 of Panretin-treated patients	Open, non-controlled, follow-up of above study

Abbreviations: BID, twice daily; TID, three times a day; QID, four times daily.

Dose-response studies

These open, randomised studies in nine US study sites used a protocol which was substantially similar. Patients of at least 18 years with biopsy-proven KS and antibody to HIV confirmed by ELISA were eligible. Systemic therapy with vitamin A or other retinoid was not allowed within 3 weeks of enrolment or during the study, and vitamin A supplements were limited to 15,000 IU/day. In the same period, no systemic therapy for KS was allowed.

For each patient, a number of cutaneous lesions (3-4 matched pairs) were designated as treated (index) lesions and as untreated (control) lesions; these had not received any local/topical therapies within 4 weeks of enrolment. Patients were initially randomised to 0.05% or 0.1% gel BID with escalation to QID application from 2 weeks onwards. Further escalation from 0.05% to 0.1% gel was then allowed from week 4 to the maximum 0.1% QID regimen, according to local or systemic toxicity. Efficacy focussed on patient response using modified ACTG definitions as used in study L1057T-31 (Table 2).

Of the 115 males treated, 100 (87%) completed 4 weeks treatment; the median duration of gel application to treated lesions was 98 days (range 5-674 days). The mean number of lesions monitored was 2.3 untreated (range 2-4, median 2) and 6.6 treated (range 1-64; median 4) lesions per patient.

Response rates were 31/115 (27%) for treated lesions (complete, CR 3 and partial, PR 28) and 13/115 (11%) PR among untreated lesions. In total, 144/758 (19%) treated and 25/264 (10%) control lesions showed a CR or PR. The patient-level response rates in patients who did and did not have at least one quantifiable alitretinoin plasma level showed no significant differences, but numbers are very small. For treated lesions, responders were 2/13 (15%) *versus* 29/102 (28%) for patients taking or not taking vitamin A supplements, respectively.

The choice of 0.1% gel from Phase I/II trial results is based on studies that were primarily designed to evaluate 0.1 and 0.05% gels. These studies did not reveal any advantage in terms of safety for the lower gel concentrations tested. However, due to the open, short duration design and within-patient comparison of treated/untreated lesions the results of these studies are of limited value in supporting the choice of 0.1% gel over other strengths for Phase III trials in terms of efficacy. The choice of 0.1% gel relies mostly on general principles that the therapeutic agents used in the treatment of neoplastic disorders should be applied at the highest possible safe dose in order to maximise the potential for lesions to respond. Concerning the frequency of application, in the case of topical therapies, appropriate consideration needs to be given to the regimen applied on a per-lesion basis in order to take into account the variability between lesions. L1057T-31 provides provisional evidence that BID may not be optimal for efficacy; nevertheless the safety data from the two trials point out that TID or QID application is associated with higher rates of local intolerance. Therefore, patients should initially apply Panretin gel twice a day and the application can be increased stepwise to three or four times a day according to individual lesion tolerance, allowing no less than two weeks between frequency of application increases. Similarly, appropriate frequency of application reduction criteria has been provided if application site toxicity occurs (see SPC section 4.2, *Posology and method of administration*).

Main studies

Patients and lesions

Patients of ≥ 18 years and Karnofsky score ≥ 60, with biopsy-proven KS and ELISA-confirmed HIV antibody were eligible. In L1057T-31, six accessible lesions of ≥ 30 days or ≥ 10 mm, which had not been treated with local or topical therapies within 60 days or with systemic treatment within 30 days, including three raised lesions, were chosen as index lesions. ALRT1057-503 specified 3-8 indicator lesions of ≥ 10 × 2 mm which had received no local treatment at any time. Patients who switched from vehicle to active gel or who entered the open-label phase having previously withdrawn due to progressive disease (PD) had new baseline measurements established for index lesions which were then used for the determination of responses.

Treatment

Patients in L1057T-31 were randomised to 12 weeks initial treatment with 0.1% gel or vehicle applied TID, increasing to QID after 2 weeks but reducing in the event of local intolerance. Patients with PD before week 12 were crossed-over to the other group without unblinding. Patients in ALRT1057-503 were randomised to 12 weeks initial treatment with 0.1% gel or vehicle applied BID, reducing to once daily if toxicity became apparent. Patients with PD before week 12 and all others at week 12 were offered open-label active therapy for up to 36 weeks. There was no blinded cross-over in this study. In both trials, all patients who completed the blinded phase were eligible for open-label active therapy.

Patients in both trials continued to apply gel to lesions regardless of the response except in the rare circumstances of complete disappearance of a lesion. Also, patients were allowed to apply gel to any other lesions, designated as *non-index*, as they wished, for which responses were not specifically monitored.

Only moisturisers and mineral oils were allowed as topical applications during the study. Within 30 days or during the study, no concurrent topical or systemic retinoid therapies (including β-carotene), were allowed and vitamin A intake was limited to 15,000 IU/day; L1057-503 specified no prior

treatment (at any time) with vitamin A > 15,000 IU/day or retinoids. There were no dietary restrictions.

Objectives and analysis

The primary efficacy endpoint was best overall response during the initial blinded phase of the study. A responder was defined by ≥ 50% decrease in aggregate area, or complete flattening of ≥ 50% of raised baseline lesions or flattening of ≥ 75% of nodular lesions (Table 2).

An interim analysis was planned for the initial blinded phase in both studies. In L1057T-31, this was when 100 patients had reached week 12. It consisted of an analysis of the response rate in the vehicle group only and was performed by an outside contractor. The analysis prompted for the study sample size to be increased. In ALRT1057-503, an interim efficacy analysis done on 82 patients documented an extreme difference in favour of the active gel. Accrual was then halted, by which time 134 patients had been enrolled.

Table 2. Best overall and index lesion response evaluation

Best overall response evaluation	
CR	All index lesions registered as either CR or CCR
CCR	All lesions registered as CCR
PR	One of the following compared to baseline measurements: a ≥ 50% decrease in the aggregate area of all the index lesions; a ≥ 50% decrease in the number of raised lesions; a ≥ 75% decrease in the number of nodular lesions to either macules or plaques.
SD	None of the criteria for either response or progressive disease
PD	One of the following compared to baseline measurements: a ≥ 25% increase in the aggregate area of all the index lesions; a ≥ 25% increase in the number of raised nodular or plaque-like lesions compared to baseline.
Index lesion response evaluation	
CR	Decrease in the lesion area to zero and no evidence of KS (biopsy).
CCR	Decrease in the lesion area to zero (not biopsy confirmed).
PR	A decrease in the lesion area by 50% or more from baseline without concurrent increase in lesion height or complete flattening of a lesion raised at baseline without a concurrent increase in area by ≥ 25% from baseline.
SD	Any classification not meeting CR, CCR, PR or PD.
PD	Increase in lesion area by 25% or more from baseline value or an increase in height of a lesion.

Abbreviations: CR, complete response; CCR, clinical complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Results of L1057T-31

Of the 134 patients randomised to each group, 96 active and 102 vehicle group patients completed 12 weeks of blinded therapy. The median total number of lesions (*i.e.*, index and non-index) treated with Panretin by the 117/134 patients with available data was 10 (range 6-88). Only one patient (active group) showed a CR by week 12 but PR were seen in 46/134 (34%) for active and 24/134 (18%) for vehicle group patients with median time to first response of 34 and 33 days respectively.

For the primary efficacy endpoint of best overall response according to modified ACTG criteria, the difference favouring alitretinoin gel was statistically significant (*p*-value for Fisher's exact test = 0.002). This treatment comparison remained statistically significant after adjustment for baseline CD_4 and raised lesion counts.

Individual lesions response rates (PR + CR) up to week 12 were 227/803 (28%) for active and 100/803 (13%) for vehicle gels; 74/134 (55%) patients on active gel compared to 31% vehicle group patients had at least one lesion show a PR while 9% and 3%, respectively, had at least one lesional CR. The Physicians Global Assessments showed CCR+PR response rates (complete clearance except for residual hemosiderin pigmentation or disease remaining with an approximately 50-90% improvement) of 20% for active *versus* 4% for vehicle group patients; the majority of patients had stable disease (105 active and 110 vehicle). Quality of life scores showed superiority for active versus vehicle treatment for patients who *completed* the blinded phase.

Disease progression in the blinded phase was documented in 20/134 (15%) active gel and 31/134 (23%) vehicle group patients, with median times to progression of 64 days and 47 days, respectively. Also, 3/47 and 1/24 of week 12 responders subsequently relapsed with median duration of response (taken from the date of first documented response to the date of documented disease relapse or last assessment for patients still in response) of 55 days in the active group and 57 days for vehicle group responders and median duration of disease control of 91 and 99 days, respectively.

For 13% per group taking vitamin A-containing supplements, 9/17 (53%) active gel and 5/17 (29%) vehicle patients responded whereas 38/117 (33%) active gel and 19/117 (16%) not taking supplements were considered responders. Similarly, 37% of lesions in active gel group patients who took supplements and 27% in other patients responded; rates in the vehicle group were 19% and 12%, respectively. Of the 128 patients (balanced across groups) who took antiviral agents (*i.e.,* other than antiretrovirals), most received acyclovir and had slightly higher response rates compared to those in either treatment group who did not receive acyclovir (40% compared to 32% in the Panretin group and 22% compared to 16% in the vehicle group).

Ultimately, 184 (91 active and 93 vehicle) patients entered the open treatment phase. There were 37 non-responders to Panretin in the blinded phase who did not enter the open-label phase, of whom four had experienced a drug-related adverse events and six had progression of treated and/or untreated lesions. Among the 28/37 with a post-baseline assessment, seven had seen a reduction in raised index lesions but 19 showed no change and two an increase. In contrast, among 50 non-responders to Panretin who entered the open-label phase, 30 (60%) had experienced a reduction in the number of raised lesions, 16 had no change and only 4/50 had seen an increase in raised lesions.

Among the 184, six CRs occurred (3%) during long-term treatment and 103/184 (56%) showed a PR. Response rate according to the last recorded application frequency was 5/25 (20%) at BID, 9/129 (7%) at TID and 31/94 (33%) at QID. During the entire trial, 67/234 (29%) had a CR to Panretin in at least one index lesion and 9% had four or more lesions which showed a CR to Panretin; also, 141/234 (60%) of patients had a PR in at least one lesion at any stage of the trials and 36% had a PR in four or more lesions.

Among 110 patients who had a response to Panretin at any stage, the Kaplan-Meier projection for median time to response was 14 weeks, by which time 83/110 (75%) had met response criteria, with 99/110 (90%) responding by week 20. For the 558 responding lesions, the projected median time to lesion response was 18 weeks; 502/558 (90%) had actually responded by day 155 (week 22). Overall, 23/142 (16%) of PR index lesions that eventually converted to CR had done so by week 12; the remaining 119 converted with a median duration of therapy of 24 weeks. Among 29/110 responders assessed after discontinuation, four relapsed at 1, 1.5, 3 and 14 months. With a 121/172 (70%) by-lesion response rate prior to discontinuation, 94/121 (78%) remained in response and 27 (22%) either showed a 25% or greater increase in area from the re-set baseline or changed from flat to raised.

Results of ALRT1057-503/4

There were 134 male patients enrolled at 22 non-US and US centres (accrual per site range: 1-38), of whom 62 were initially randomly assigned to active and 72 to vehicle gel. For the primary efficacy endpoint, the overall response rate was 23/62 (37%, 1 CCR and 22 PR) in the active group which was statistically significantly superior to the response rate of 5/72 (7%, 5 PR) for vehicle group patients.

The study was terminated early after a pre-planned interim analysis on efficacy had been performed on the first 82 patients. The extreme *p*-value observed in the interim analysis was very close to that appropriate for rejecting the hypothesis of no difference at an overall 5% significance level.

The median time to onset of first response was 29 days for the active group and 40 days for the vehicle group responders. There were 9/62 (15%) active group and 3% vehicle group patients who had at least one index lesion completely resolve while 37% compared to 26% had at least one lesion show a PR. Individual lesion responses (CR+PR) were 91/271 (34%) for active group versus 34/303 (11%) for vehicle. Progression rates were 19% for active gel and 35% for vehicle; progression occurred at medians of 68 days and 57 days, respectively. Duration of disease control was 89 days for active and 99 days for vehicle group responders.

There were 32% Panretin and 49% vehicle group patients who received at least one anti-viral agent; the majority received acyclovir among whom the response rates were slightly higher compared to

those in either treatment group who did not receive acyclovir (54% versus 33% in the active group and 12% compared to 4% in the vehicle group).

There were 99 patients, 41 (66%) initially assigned to active and 58 (81%) to vehicle, who entered the open-label study, of whom 3 and 10, respectively, had previously withdrawn from the blinded phase. There were 17 non-responders to Panretin who did not continue (2 withdrew because of a drug-related adverse events and 3 had progressive disease of treated and/or untreated lesions; only 2 had seen a moderate or marked response, 10 showed no change and one a reduction in raised lesions). Also, 4/23 responders did not continue (2 had a PR, 1 had progressive disease in untreated lesions and 1 had severe dermatitis and required systemic therapy for KS). However, 22 non-responders chose to continue into the open-label phase, of which 13 had no change in raised lesions, six had a reduction and three an increase.

Among the patients who opted to receive open-label active gel, 44/99 (44%) achieved a best response of CR (4) or PR (40). Overall, 36/120 (30%) of patients had a CR to Panretin in at least one index lesion and 6% had four or more lesions that showed a CR to Panretin. Also, 73/120 (61%) had at least one lesion show PR at any stage of the trials and 23% had a PR in four or more lesions.

Discussion on clinical efficacy

Study design

Despite the double-blind design of the two pivotal trials the adverse events associated with the active treatment made investigators' awareness of assigned treatment more probable than unawareness. This may have conditioned the assessment of the "soft" subjective variables chosen as clinical endpoints of the studies.

Lesions

It is difficult to establish to what extent the results obtained on treated index lesions can be extrapolated to non-treated lesions although index lesions at different anatomical sites were chosen and the protocols explicitly specified that representative lesions were to be selected. However, even if the effect observed in index lesions cannot be extrapolated to all lesions, this does not preclude that the effect observed in individual lesions may result in improved cosmetic outcome, which is of clinical relevance in this patient population.

CRs and PRs by patient

Results from both Phase III trials showed that active gel was superior to vehicle for the primary efficacy variable (by 17% and 30% in the two trials) and that rates of progression were lower (by 8 and 13% in the two studies) with active treatment but almost all responses were partial. One-third (36/110) responders relapsed, all but four still being on active treatment. Trials did not allow for assessment of responses *versus* vehicle beyond 12 weeks, which makes it impossible to discern the contribution which better systemic management of HIV disease might have had on the cutaneous severity of KS over the two year period of clinical trial conduct. However, 75% of patients were on at least three antiviral regimens during the studies. The trials did evaluate the CR and PR rates with Panretin in comparison with other local treatments.

CRs and PRs by lesion

For cumulative responses, 30% of all patients had a CR to Panretin in at least one lesion (< 10% had CRs in four or more lesions) while 60% had at least one PR (23-36% per trial had four or more). These data must be reviewed in the light of patient status at week 12, which suggested that those who had already seen a reduction in raised lesions were most likely to continue to respond with continued use.

Dose regimens

The optimal concentration of alitretinoin in gel for the treatment of KS lesions and the optimal frequency of application have been chosen based on general principles. Frequency of treatment application should be determined by lesion. Patients should initially apply Panretin twice daily and, in the absence of application site toxicity for a lesion, a stepwise increase to TID or QID allowing no less than 2 weeks between application frequency escalations is recommended. Criteria for modifying the

frequency of application based on application site toxicity have been provided. Treatment duration should also be determined by the response of individual lesions. If no response for a lesion has been observed within 12 weeks of the first application, then treatment for that lesion should be discontinued (see SPC section 4.2, *Posology and method of administration*).

Clinical safety

Patient exposure

The safety database (first cut-off at 6/7/98 was later updated to 7/99) included information on 469 patients with AIDS-related KS who were exposed to Panretin gel, of whom 439 received the 0.1% strength at some time. There were 208 patients assigned to vehicle gel in the trials, of which 143 went on to receive active treatment in the open extension phase, and 15 switched during the double-blind phase; two patients switched from active to vehicle. Only two females were treated; this reflects the gender distribution of KS. The age range was 25-71 years (median 38 years).

Adverse events

In Phase I/II, in which patients served as their own controls, the incidence of drug-related rash was 83%; severity was mild or moderate in 79/95 cases. Other local affects such as pain (22%), skin disorder (18%), dry skin (10%), ulcerated skin (9%), itching (6%) was also observed. Skin oedema, skin discoloration or haemorrhage were observed in < 5% of patients. The incidences of the different types of toxicity were similar for 0.1% compared to 0.05% gel. Also, the frequency of application of 0.1% gel did not show to be related to the incidence of local AEs.

In the blinded phases of the two Phase III trials, the incidences of rash (75% active versus 18% and 45% active versus 17% in the two studies), pruritus, skin disorder, paraesthesia, pain and exfoliative dermatitis were notably higher in the active groups in both studies. Combining Phase III trials, those AEs considered to be drug-related also showed marked differences between groups for patients reporting rash (66% versus 11%), pain (24 versus 8%), skin disorder (12 versus 0%), pruritus (12% versus 5%), exfoliative dermatitis (as above), and other skin problems.

During long-term treatment (>16 weeks) of 254 patients, rash was by far the commonest event (180/254, 71%). Rashes were mild in 124 (49%) patients, moderate in 80 (31%) and severe in 23 (9%) of patients. Additional analyses showed that the total incidence of rash was higher among those treated for >16 weeks (82% compared to 57%), with a higher incidence of moderately severe rash (43% compared to 29%) but the same incidence of severe rash (10%). Whereas the first onset of rash was predominantly before week 16, severity tended to progress from mild to moderate with time. From narratives on those 22 patients who experienced severe rash in L1057T-31 and the 11 similar patients in 503/504, 30% reached severe grade during QID applications, 24% during TID and 36% during BID; most (27/33) patients were managed by at least one dose suspension but it is difficult to be precise about management due to changes in frequencies of application over time in many patients. There was documentation of resolution in 74% of cases, with a median time to resolution of 64 days (range 2-761 days). Skin disorder was reported in 15%, pain in 14%, pruritus in 12% and exfoliative dermatitis in 9%.

For pain and pruritus, total incidences were higher in patients treated > 16 weeks but the difference was most marked for pruritus (24% compared to 8%) and for both combined (19% compared to 7%). First onset of pain and/or pruritus was more likely to be within the first 16 weeks but the data still indicate some progression of severity with time. It seems that 38/53 events were documented to have resolved and not to have reappeared on restarting applications; 11 AEs recurred, including erythema, pruritus, irritation, dryness and exfoliation.

The duration of most common application site AEs has been assessed for one of the Phase III studies (L1057T-31). In this study, 74% of the adverse events of rash were known to have resolved with a median time to resolution of 64 days (range 2 to 761 days) without regard to whether any dose modifications were initiated during the event. Over the same period, 84% of the adverse events of pain were known to have resolved with a median time to resolution of 29 days (range 1 to 381 days).

Drug interaction studies are missing but the applicant presented AE data for subsets of patients who applied alitretinoin while taking several triazoles, macrolides, or indinavir. The numbers were small

but the data suggested that the AE reporting rates were not affected by concomitant systemic administration of these agents.

In Phases I/II and III, there were no treatment-emergent trends in any laboratory tests over time. Individual abnormalities were considered to be consistent with the underlying disease and its complications.

Withdrawals due to adverse events

In the Phase I/II trials, 9% of patients withdrew due to an AE; all these events were application site problems. In Phase III, 37/469 (8%) of patients withdrew while on active gel, of whom 23 withdrew because of rash and seven due to pain. No other event precipitated withdrawal of more than two patients. Although 18 patients initially assigned vehicle withdrew (9%), only four patients withdrew while on vehicle gel (2%) - two for lymphoma-like reaction, one for pain and one for asthenia.

Serious adverse events and deaths

No SAEs reported in Phase I/II trials were considered possibly or probably related to therapy. In Phase III trials, a wide variety of SAEs was reported as might be expected in this study population; commonest events in both groups were infections and progression of KS. In addition, few SAEs precipitated withdrawal from study. There were three deaths in Phase I/II trials, and 19 deaths in Phase III trials. The commonest causes of death were sepsis or progressive AIDS. No deaths appeared to be drug-related.

Discussion on clinical safety

The true exposure to alitretinoin was difficult to assess because although the total number of lesions treated (index and non-index) was recorded in one trial, durations were not recorded for all lesions.

For a medication, which would be expected to improve cosmetic outcome as a result of amelioration of skin lesions, the high incidences of rash (most often accompanied by pain and pruritus) and skin disorders were of some concern. In addition, an excess incidence of paraesthesia was observed. However, the duration of these adverse events needs to be compared to the duration of response, and most events were mild to moderate in intensity.

Association between local adverse reactions and body site, particularly for intertriginous areas and for the face, were not available and this again supports the need for by lesion adjustments in frequency of application. Similarly, there are no data regarding tolerance of non-lesional (surrounding) skin to Panretin because toxicity was recorded as a composite assessment of the overall degree of irritation observed. Dose reduction instructions, which take into account variations the tolerance of the skin surrounding individual lesions should it come into contact with the gel in the course of treatment, have been included (see SPC section 4.2, *Posology and method of administration*).

5. Overall conclusion and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Preclinical pharmacology and toxicology

At the time of development, adequate animal models of KS in which to test 9-cis-RA were lacking. Alitretinoin did not appear to be cytotoxic or apoptogenic on KS cells *in vitro*. Most of the pre-clinical studies presented are derived from generalising data obtained in different tumours to the KS setting and need to be interpreted with caution.

One toxicity aspect that is of potential clinical relevance is the well-established teratogenicity of retinoids as confirmed by the data presented. Therefore, the use of Panretin is contraindicated in pregnancy and lactation and this reflected in the SPC (see section 4.3 *Contraindications* and 5.3 *Preclinical safety data*).

In cell-based *in vitro* assays, alitretinoin showed weak phototoxic potential. Patients are advised to avoid direct sunlight (see SPC 4.4**,** *Special warnings and special precautions for use*)

Efficacy

Both Phase III trials suggested that active gel was superior to vehicle for the primary efficacy variable (by 17% and 30% in the two trials) and that rates of progression were lower (by 8 and 13% in the two studies) with active treatment. However, almost all responses were partial.

It is difficult to establish to what extent the results obtained on treated index lesions can be extrapolated to the rest of the lesions. Even if such an extrapolation cannot be generally assumed, in the absence of any other treatment options, the demonstrated efficacy of Panretin may still result in improved cosmetic outcome that is of clinical relevance in this patient population.

The trials did not allow for evaluating the CR and PR rates with Panretin in comparison with other local treatments, particularly radiotherapy. Therefore, the use of Panretin is only indicated in those patients in whom radiotherapy is no longer an appropriate treatment option.

Frequency of treatment application should be determined separately for each individual by lesion. Patients should initially apply BID applications and, in the absence of application site toxicity for a lesion, a stepwise increase to TID or QID allowing no less than 2 weeks between application frequency escalations, is recommended. Dose modifications to ameliorate application site toxicity have been provided. Treatment duration should also be determined on a by lesion fashion. If no response for a lesion has been observed within 12 weeks of the first application, then treatment for that lesion should be discontinued (see SPC section 4.2, *Posology and method of administration*).

Safety

There were some concerns regarding the degree of local intolerance of Panretin and that the data suggested an increasing incidence of rashes of moderate severity with longer-term treatment. However, in this treatment population and in the absence of other established treatment modalities, the severity and duration of local intolerance to Panretin compare favourably with the duration of response and the expected benefits in terms of cosmetic outcome. Frequency of application reduction criteria due to toxicity as well as treatment duration need to be determined separately for individual lesions (see SPC section 4.2, *Posology and method of administration*).

Benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Panretin gel was favourable in the treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (KS) when:

- lesions are not ulcerated or lymphoedematous, and
- treatment of visceral KS is not required, and
- lesions are not responding to systemic antiretroviral therapy, and
- radiotherapy or chemotherapy are not appropriate.