ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Panretin 0.1 % gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains 1 mg alitretinoin (0.1%).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.
Clear yellow gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Panretin gel is indicated for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (KS) when:

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

4.2 Posology and method of administration

Posology

Panretin therapy should only be initiated and maintained by specialist physicians experienced in the treatment of patients with KS.

Men
Patients should apply Panretin to cutaneous KS lesions using sufficient gel so as to cover each lesion with a generous coating.

Frequency of application
Patients should initially apply Panretin twice a day to cutaneous KS lesions. 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 dose increases. The frequency of application should be adjusted for each lesion independently. If application site toxicity occurs, the application frequency can be reduced as described below. There are no data on the efficacy of Panretin applied less frequently than twice daily.

Local dermal irritation may be graded according to the five-point scale shown in Table 1. Guidelines for treatment adjustments necessitated by local dermal treatment-related toxicity are specified in Table 2.

Table 1 Grading of local dermal irritation

GRADE	DEFINING CLINICAL SIGNS
0 = No reaction	None
1 = Mild	Definite pink to red coloration
2 = Moderate	Increased redness, possible oedema
3 = Severe	Very red, with oedema, with or without vesiculation
4 = Very severe	Deep red, swelling and oedema with or without signs of bullae formation and necrosis

Table 2 Adjustment guidelines for treatment-limiting toxicity

LOCAL DERMAL IRRITATION (Graded per Table 1)	TREATMENT ADJUSTMENTS
Grade 0, 1 or 2	No action required except continued monitoring.
Grade 3	Treatment frequency for that lesion should be reduced or suspended. When dermal irritation improves to Grade 0 or 1, treatment may be restarted at twice daily, increasing every two weeks as tolerated.
Grade 4	As for Grade 3 irritation. However, treatment should not be restarted if Grade 4 toxicity occurred at an application frequency of less than twice a day.

Duration of application
It is recommended that Panretin should be applied to lesions for an initial period of up to 12 weeks. Treatment of lesions that have not shown a decrease in area and/or height by week 12 should be discontinued.
For those lesions that have shown a decrease in height and/or area by week 12, applications may be continued providing that there is continued improvement or at least maintenance of the response and that the product continues to be tolerated.
Treatment of any lesion that has fully resolved on clinical assessment should be discontinued.

Precautions to be taken before handling or administering the medicinal product
Patients should wash their hands before and after applications; it is not necessary to wear gloves. The gel must be allowed to dry for three to five minutes before covering with clothing. Occlusive dressings should be avoided.
Care must be taken to avoid application of the gel to normal skin surrounding the lesions.
Gel should not be applied on or near eyes or mucosal surfaces of the body. Showering, bathing, or swimming for at least three hours after any application should be avoided.

Women
Safety and effectiveness in women have not been established because of the paucity of clinical data. AIDS-related Kaposi's sarcoma is infrequent in women.

Paediatric population
The safety and efficacy of Panretin gel in children under 18 years has not been established.
No data are available.
Panretin is not approved for use in children and adolescents under 18 years of age.

Elderly men
There are no specific recommendations for use in elderly men (above 65 years of age). AIDS-related Kaposi's sarcoma is infrequent in this population.

Patients with renal or hepatic impairment
There are no data regarding the use of Panretin gel in patients with renal insufficiency or liver disease. Pharmacokinetic studies indicate that the range and frequency of detection of quantifiable 9-*cis*-retinoic acid plasma concentrations in patients with KS after application of the medicinal product were comparable to the range and frequency of detection of quantifiable plasma concentrations of circulating, naturally-occurring 9-*cis*-retinoic acid in untreated individuals (see section 5.2). On a

theoretical basis, no dose adjustment is necessary in patients with renal insufficiency or liver disease, but these patients should be closely monitored and treatment frequency reduced, or withdrawn, if they experience adverse effects.

4.3 Contraindications

- Hypersensitivity to retinoids in general, to the active substance alitretinoin or to any of the excipients listed in section 6.1.
- Pregnancy and breast-feeding (see section 4.6).
- Women planning a pregnancy.
- Treatment of KS lesions in close proximity to other skin disorders.

4.4 Special warnings and precautions for use

Retinoids as a class have been associated with photosensitivity. There were no reports of photosensitivity associated with the use of Panretin gel in the clinical studies. However, patients must be cautioned to minimise exposure of treated areas to sunlight or other ultraviolet (UV) light. (see section 5.3).

It is recommended that daily dietary intake of vitamin A should not exceed the Recommended Dietary Intake value.

Alitretinoin may cause harm to the foetus. Women of child-bearing potential must use a reliable form of contraception during treatment with Panretin gel (see section 4.6) and until one month after cessation of treatment.

4.5 Interaction with other medicinal products and other forms of interaction

The use of other topical products on Panretin treated KS lesions should be avoided. Mineral oil may be used between Panretin applications in order to help prevent excessive dryness or itching. However, mineral oil should not be applied for at least two hours before or after the application of Panretin.

It is not recommended for patients to apply Panretin gel concurrently with products that contain *N*,*N*-diethyl-*m*-toluamide (DEET), a common component of insect repellent products. Animal toxicology studies showed increased DEET toxicity when DEET was included as part of the formulation.

The range and frequency of detection of quantifiable plasma 9-*cis*-retinoic acid concentrations in patients with KS applying the medicinal product to up to 64 lesions were comparable to respective values in untreated patients. Therefore, there is a low potential for interactions with systemic medicinal products.

There was no clinical evidence in the vehicle-controlled studies of interactions with systemic antiretroviral agents, including protease inhibitors; macrolide antibiotics and azole antifungals. While no data are available, it is possible that co-administration of medicinal products which induce CYP isozymes may reduce circulating levels of alitretinoin, with a possible negative effect on the efficacy of Panretin gel.

4.6 Fertility, pregnancy and lactation

<u>Women of child-bearing potential</u>

Women of child-bearing potential must use effective contraception during, and up to one month after cessation of treatment.

Men using Panretin should take precautions to ensure that their female partners do not become pregnant.

Pregnancy

Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information topically administered retinoids are generally assumed to result in low systemic exposure due to minimal dermal absorption. However there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure. In rabbits, alitretinoin was shown to be teratogenic at a dose which resulted in plasma concentrations about 60 times the highest observed plasma concentration in male patients with KS following topical application of the gel. However, it is not currently certain to what extent topical treatment with Panretin gel would increase 9-*cis*-retinoic acid plasma concentrations, in women with KS above naturally occurring levels; therefore, Panretin is contraindicated (see section 4.3) in pregnancy, or in women planning a pregnancy. If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

Breast-feeding

It is not known whether this medicinal product is excreted in human milk. Based on the plasma concentrations observed in patients, milk concentrations of 9-*cis*-retinoic acid probably pose a low risk for the infant. However, because of the potential for undesirable effects from Panretin gel in infants being breast-fed, mothers must discontinue breast-feeding prior to using the medicinal product and not initiate breast-feeding while using the medicinal product.

Care should be taken not to bring the neonate into skin contact with areas to which Panretin has been recently applied. It is recommended that HIV-infected mothers do not breast-feed their children to exclude the risk of transmission of the virus.

Fertility

No specific studies on fertility have been conducted in men or women. However, alitretinoin is teratogenic so both men and women should take adequate precautions to avoid female partners becoming pregnant.

4.7 Effects on ability to drive and use machines

Panretin gel is for cutaneous use and is unlikely to have an effect on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events associated with the use of Panretin gel in AIDS-related KS occurred almost exclusively at the site of application. The dermal toxicity typically begins as erythema; with continued application of Panretin gel erythema may increase and oedema may develop. Dermal toxicity may become treatment-limiting, with intense erythema, oedema, and vesiculation. When applying Panretin gel, 69.1% of patients experienced adverse drug reactions at the application site.

Table 3 shows the following application-site drug-related adverse reactions were reported during clinical studies in patients with KS. The frequency of adverse events are classified as very common (≥1/10), common (≥1/100 to <1/10), and uncommon (≥1/1,000 to <1/100). Adverse events include verbatim terms in parentheses.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3 Adverse reactions reported in patients in clinical trials

System Organ Class (MedDRA terminology)	**Very common**	**Common**	**Uncommon**
Blood and lymphatic system disorders			Lymphadenopathy
Nervous system disorders		Paraesthesia (stinging, tingling)	
Vascular disorders		Haemorrhage (bleeding at or around lesions), Oedema (oedema, swelling, inflammation), Peripheral oedema	Phlebitis, Vascular disorder
Skin and subcutaneous tissue disorder	Skin disorder (cracking, scab, crusting, excoriation, drainage, oozing), Rash (erythema, redness, scaling, irritation, dermatitis), Pruritus (itching, pruritus)	Skin ulcer, Serous drainage, Exfoliative dermatitis (flaking, peeling, desquamation, exfoliation), Skin discoloration (brown discoloration, surrounding hyperpigmentation, paler), Dry skin	Cellulitis, Vesiculobullous rash, Maculopapular rash, Allergic reaction
General disorders and administration site conditions	Pain (burning, pain, soreness)		Infection, including bacterial infection

The safety of Panretin gel has been assessed in clinical studies of more than 469 patients with AIDS-related KS, 439 of whom were treated with an alitretinoin concentration of 0.1%.

The incidence of drug-related skin disorder, skin ulcer, pain and rash appeared to be greater in patients applying Panretin gel four times daily than in those applying it less frequently. However, the incidence of other equally common drug-related adverse events such as pruritus, oedema, exfoliative dermatitis and dry skin did not appear to increase as a function of the frequency of application.

The incidence of mild/moderate rash (all events regardless of causality) was less in patients treated for less than 16 weeks than in those treated for 16 weeks or more (mild, 33% v 63%; moderate, 29% v 43%). The incidence of severe skin rash was independent of the duration of treatment (10% in both cases).

Local dermal toxicity associated with Panretin gel therapy generally resolved with treatment adjustment or discontinuation (see section 4.2).

Only two serious adverse reactions were reported (sepsis and cellulitis in the same patient).

The adverse events seen with Panretin gel are similar to those seen with other topical retinoids. It is unlikely that the undesirable systemic side effects associated with oral retinoids will be observed with the use of Panretin gel because the range and frequency of quantifiable 9-*cis*-retinoic acid plasma levels concentrations after application of the medicinal product were comparable to the range and frequency of quantifiable plasma concentrations of circulating, naturally occurring 9-*cis*-retinoic acid in untreated individuals.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

Systemic toxicity following acute overdose with topical application of Panretin gel is unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, ATC code: LO1XX22

Although the molecular action of alitretinoin is thought to be mediated through interaction with the retinoid receptors, the exact mechanism of action of this medicinal product in the topical treatment of cutaneous lesions of AIDS-related KS is unknown. Alitretinoin (9-*cis*-retinoic acid), a naturally-occurring endogenous hormone related to vitamin A, binds to and activates all known intracellular retinoid receptor subtypes (RARα, RARβ, RARγ, RXRα, RXRβ, RXRγ). Once activated, these receptors function as ligand dependent transcription factors that regulate the expression of specific genes. The regulation of gene expression by alitretinoin controls the process of cellular differentiation and proliferation in both normal and neoplastic cells. The efficacy of Panretin gel in treating KS lesions may be related to the demonstrated ability of alitretinoin to inhibit the *in vitro* growth of KS cells.

Panretin gel can be expected to have local therapeutic effects only and it has no role in the prevention or treatment of visceral KS.

Two controlled, multicentre, randomised, double blind parallel group, Phase III studies provided the data for Panretin gel in the treatment of index cutaneous lesions of KS (Table 4). The patient response rate was evaluated using the AIDS Clinical Trials Group (ACTG) criteria for lesion response in KS. Study 1 included an open-label phase, in which patients themselves elected to enroll. Study 2 was followed by an open label study (Study 2a), which included only patients electing to continue from Study 2.

Table 4 Best response according to ACTG criteria for vehicle controlled phase

	Study 1 (TID, QID)[1]		Study 2 (BD)[2]	
	Panretin N= 134	Vehicle N=134	Panretin N=62	Vehicle N=72
Clinical Complete Response (CCR) %	0.7	0.0	1.6	0.0
Partial Response (PR) %	34.3	17.9	35.5	6.9
Stable Disease %	50.0	59.0	43.5	58.3
Progressive Disease %	14.9	23.1	19.4	34.7
Overall Response %	35.1	17.9 p=0.002	37.1	6.9 p= 0.00003

1. Protocol-specified dose regimen was application three times a day (TID) escalating to four times a day (QID) after two weeks, with downward adjustments for toxicity.
2. Protocol-specified dose regimen was application twice a day (BD) only, with downward adjustments for toxicity.

In the open label phase of Study 1 (N = 184), the overall response rate increased to 66.7%. In Study 2a (N = 99), the overall response rate increased to 56.1%.

In study 1, of 110 responding patients, 36 (33%) relapsed, while all but four still being on active treatment.

Response rates were analysed both by the patient as the unit of analysis and by the lesion. **Table 5** provides the individual lesion response rates for patients being treated with Panretin gel in the Phase III studies.

Table 5 Index/indicator lesion[1] responses within patients during the first 12 weeks on study in initial blinded phase

	Patients with given number of index/indicator lesion responses (CCR or PR)			
	Study 1		Study 2	
Number of Responding	Panretin (N=134)	Vehicle (N=134)	Panretin (N=62)	Vehicle (N=72)
Lesions[2,3]	N %[4]	N %[4]	N %[4]	N %[4]
At Least One	73 (54.5%)	42 (31.3%)	33 (53.2%)	21 (29.2%)
At Least Four	27 (20.1%)	8 (6.0%)	8 (12.9%)	2 (2.8%)

1. Study 1, 6 index lesions; Study 2, up to 8 index lesions
2. Each index lesion assessed individually for response.
3. Lesions responding during the first 12 weeks on study, initial blinded phase, confirmed over at least four study weeks (confirmation of response may have occurred after 12 weeks for some lesions in Study 1).
4. Percentages calculated as number of patients with responding lesions divided by total number of patients in the initial blinded phase.

In one trial, 29% of the lesions that had reached a partial response (PR) but had not attained clinical complete response (CCR) within the first 12 weeks of treatment developed a CCR during continuing treatment beyond 12 weeks. The projected time for lesions that were in partial response (PR) to later attain clinical complete response (CCR) was 168 days. It is recommended that Panretin gel should be applied for an initial treatment period of up to 12 weeks. In lesions that have responded to treatment during this time, application may be continued provided that the response improves or is maintained and the product continues to be tolerated. If a complete response of a lesion occurs, no further application of Panretin gel should be made to the responding lesion.

There are no data regarding the efficacy of Panretin gel when applied to complicated lesions (e.g., when lymphoedema is present).

5.2 Pharmacokinetic properties

Plasma concentrations of 9-*cis*-retinoic acid were evaluated during clinical studies in patients with cutaneous lesions of AIDS-related KS after repeated multiple-daily dose application of Panretin gel for up to 60 weeks. A subset of these patients were followed during treatment of up to 64 lesions (range 4-64, median 11.5 lesions) for up to 44 weeks (range 2-44, median 15 weeks). In this latter group, the range and frequency of detection of quantifiable 9-*cis*-retinoic acid plasma concentrations in patients with KS after application of the medicinal product were comparable to the range and frequency of detection of quantifiable plasma concentrations of circulating, naturally-occurring 9-*cis*-retinoic acid in untreated individuals.

5.3 Preclinical safety data

Toxicology

Three doses of alitretinoin (0.01%, 0.05%, or 0.5%) in a topical gel formulation were given to rats in a 28-day dermal toxicology study. Observed effects at the application site included erythema, epidermal thickening, scaling and loosening of the stratum corneum. Clinical pathology evaluations revealed significant increases in absolute polymorphonuclear leukocyte counts, monocyte counts, percentage of

monocytes and decreases in percentage of lymphocyte differential white blood cell counts on day 29 of rats treated with alitretinoin 0.5% gel. Clinical chemistry evaluations revealed biologically relevant significant increases in the mean BUN and alkaline phosphatase values in females after the 28-day treatment. Serum LDL was increased in both male and female groups at Day 29. There were no biologically relevant haematology differences or serum chemistry differences after the 14-day period. Observed increases in mean heart-to-final body weight differences were attributed principally to the difference in the terminal body weights. Following treatment with alitretinoin 0.5% gel, mean plasma concentrations in the female rats were generally below the lower limit of quantitation (5 nMol) and mean plasma concentrations in the male rats were about 200 nMol. In contrast to these findings in rats, plasma concentrations of 9-*cis*-retinoic acid in patients with KS applying Panretin gel never exceeded 0.638 ng/ml (2.13 nMol). This level is about 1/100 the mean concentration measured in male rats.

Genotoxicity

Alitretinoin was studied for genotoxic potential using the Ames test, the *in vivo* mouse micronucleus assay, the chromosomal aberration test in human lymphocytes, and the CHO cell mutation test. The medicinal product was not genotoxic.

Carcinogenesis, mutagenesis, impairment of fertility

Studies have not been performed to determine the carcinogenic potential of alitretinoin. However, the mutagenic potential has been evaluated, and alitretinoin has tested negative in the Ames test, the *in vivo* mouse micronucleus assay, the chromosomal aberration test in human lymphocytes, and the CHO cell mutation test.

Teratogenicity

In an oral dose-ranging study in rabbits, alitretinoin induced gross malformations at a dose 35 times the topical human dose. This dose in rabbits resulted in plasma concentrations more than 60 times the highest observed plasma concentration in patients with KS following topical application of Panretin gel. No gross malformations were observed following oral administration to rabbits of doses 12 times the human topical dose (which resulted in plasma concentrations 60 times the highest observed plasma concentration in patients with KS following topical application of the gel). However, an increased rate of fused sternebrae was observed.

Phototoxicity

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 and is subject to photodegradation to other isomers (predominantly all-*trans*-retinoic acid). Alitretinoin was shown to have a weak potential to be a photo-irritant based on histidine and photoprotein binding. In cell-based *in vitro* assays, alitretinoin showed weak phototoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Macrogol 400
Hydroxypropylcellulose
Butylhydroxytoluene

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. The use of other topical products on treated KS lesions should be avoided. Panretin gel should not be used concurrently with products containing DEET.

6.3 Shelf life

Unopened: 3 years.

In-use: Any remaining tube should be discarded 90 days after first opening.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original container in order to protect from light.
Keep the container tightly closed.
After opening the tube for application, the tube cap must be replaced and closed tightly to provide an airtight seal. Opened tubes of Panretin gel must not be stored above 25°C, and should be protected from exposure to strong light and heat (e.g., direct sunlight).

6.5 Nature and contents of container

Panretin gel is supplied in a multi-use 60 g epoxy-lined aluminium tube.
Each carton contains one tube of gel.

6.6 Special precautions for disposal and other handling

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

Panretin gel contains alcohol, keep away from naked flame.

7. MARKETING AUTHORISATION HOLDER

Eisai Ltd.
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/149/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 11 October 2000
Date of latest renewal: 27 September 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eisai Manufacturing Limited
European Knowledge Centre
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

• OTHER CONDITIONS

Not applicable

C SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT AND TUBE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

Panretin 0.1 % gel
alitretinoin

2. STATEMENT OF ACTIVE SUBSTANCE

1 g of gel contains 1 mg alitretinoin (0.1%).

3. LIST OF EXCIPIENTS

Also contains ethanol, macrogol 400, hydroxypropylcellulose, butylhydroxytoluene.

4. PHARMACEUTICAL FORM AND CONTENTS

Gel, 60 g

5. METHOD AND ROUTE OF ADMINISTRATION

For cutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not for application to the eyes or mucous membranes.
Contains alcohol, keep away from naked flame.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original container in order to protect from light.
Keep the container tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Ltd.
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/00/149/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Panretin gel 0.1%

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Iinformation for the user

Panretin 0.1% gel
Alitretinoin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Panretin is and what it is used for

Panretin belongs to a group of medicines that are related to vitamin A and known as retinoids.

Panretin is used in patients with AIDS-related Kaposi's sarcoma (KS) and is for the treatment of the KS lesions:
- that are on the skin only
- which have not responded to your HIV treatment
- where the skin or lesion is not broken
- where the surrounding skin is not swollen
- if your doctor thinks that other treatments are not suitable for you.

Panretin does not treat KS that is inside the body.

2. What you need to know before you use Panretin

Do not use Panretin:
- if you are allergic to alitretinoin or to similar medicines containing retinoids
- if you are allergic to any of the other ingredients of this medicine (listed in section 6)
- if you are pregnant
- if you are planning a pregnancy
- if you are breast-feeding
- on KS lesions close to any other skin complaint

Take special care with Panretin
- Panretin is not approved for use in children and adolescents under 18 years of age.
- Do not apply the gel on or near sensitive parts of your body such as eyes, nostrils, mouth, lips, vagina, tip of the penis, rectum, or anus.
- Do not apply the gel to healthy skin around a KS lesion. Panretin may cause unwanted irritation or redness on healthy skin.
- Do not use insect repellents containing DEET (*N*,*N*-diethyl-*m*-toluamide) or other products containing DEET while using Panretin.

- Avoid prolonged exposure of the treated area to sunlight or other ultraviolet (UV) light (such as tanning lamps).
- Mineral oil may be used between Panretin applications in order to help prevent excessive dryness or itching. However, mineral oil must not be applied for at least two hours before or after the application of Panretin.
- Women of child-bearing age must use an effective method of birth control while using Panretin, and for one month after finishing treatment.

Other medicines and Panretin
Avoid the use of other products on your treated KS lesions such as insect repellents that you use on your skin.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Panretin with food and drink
It is recommended that you should not eat more vitamin A in your diet than the amount suggested by your doctor.

Pregnancy
DO NOT use Panretin if you are pregnant or thinking of becoming pregnant. Your doctor can give you more information.

Breast-feeding
Do not breast-feed your baby while you are using Panretin. Care should be taken not to bring your baby into contact with areas of your skin treated recently with Panretin.

Driving and using machines
Panretin is unlikely to affect your ability to drive or use machines.

3. How to use Panretin

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

To open for the first time, use the pointed portion of the cap to puncture the metal safety seal.

How to apply Panretin: For cutaneous use (on the skin) only
Apply Panretin twice a day to start with, once in the morning and once in the evening. After that, your doctor will decide how often you should apply the gel depending on the response of your KS and any side effects.

Apply Panretin to your KS lesions using a clean finger. Place a generous coating of gel over the whole surface of each lesion that you want to treat. You do not need to rub the gel into the lesion. You need to avoid applying the gel to the healthy skin around the lesion. Carefully applying the gel only to the area of the KS lesion will help to lessen any irritation or redness that may occur. Proper application will leave some gel visible on the surface of the lesion when you are finished.

- Immediately after application, wipe the finger(s) you have used to apply the gel and any healthy skin touched by the gel with a disposable tissue. Wash your hands using soap and water and wipe the healthy skin touched by the gel.
- Allow the gel to dry for three to five minutes before covering a treated area with loose clothing. Do not cover the treated lesions with any bandage or other material.
- A mild soap is recommended when bathing or showering.
- If you think that the effect of Panretin is too strong or too weak, talk to your doctor or pharmacist.

- Avoid showering, bathing, or swimming for at least three hours after any application.
- Avoid scratching the treated areas.
- Panretin contains alcohol. Keep away from naked flame.

Your doctor will tell you how long your treatment will last.

- Do not be discouraged if you do not see immediate improvement.
- It may take up to 12 weeks for any improvement to show.
- Do not stop treatment at the first sign of improvement.
- You may need to reduce the number of daily applications, or stop using Panretin for a short while, if you develop unwanted skin effects. It is important that you consult your doctor, who will tell you what to do.

If you use more Panretin than you should
There has been no experience with overdose of Panretin.

If you forget to take Panretin
Do not use a double dose to make up for forgotten individual doses. Apply the next dose at the usual time.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist

4. Possible side effects

Like all medicines, Panretin can have side effects, although not everybody gets them. The side effects are most likely to appear at the site where Panretin was applied and typically begins as redness. With continued application of Panretin redness and irritation may increase and swelling at the site of the application may develop. If your side effects become too uncomfortable, with intense redness and irritation, rash, swelling, or pain, you should ask your doctor for advice on adjusting the dosage of your treatment. Most patients can continue to use Panretin by altering the number of times a day it is applied. Sometimes it is necessary to interrupt treatment, your doctor will inform you about this.

The following side effects have been noted on the skin where Panretin has been applied:

<u>Very common (can occur in more than 1 in 10 patients treated):</u>
Rash, scaling, irritation, redness
Cracking, scabbing, crusting, draining, oozing
Pain, burning, soreness
Itching

<u>Common (can occur in less than 1 in 10 but in more than 1 in 100 patients treated):</u>
Flaking, peeling, dry skin
Swelling, inflammation
Stinging, tingling
Bleeding
Skin discoloration
Skin ulcer

<u>Uncommon (can occur in less than 1 in 100 but in more than 1 in 1000 patients treated):</u>
Infection
Allergic reaction
Swollen lymph glands
Pale skin

If any of the side effects gets serious or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Panretin

Keep this medicine out of the sight and reach of children.

Do not use after the expiry date which is stated on the end of the tube.
Do not store above 25°C.
Store in the original container in order to protect from light.
Keep the container tightly closed. Always use the cap to close the tube tightly after each use.

After opening, use within 90 days.

The opening of the Panretin tube is covered by a metal safety seal. If this seal has been punctured or is not visible when you first open the package, DO NOT USE and return the product to your pharmacy.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Panretin contains
- The active substance is alitretinoin. 1 g of gel contains 1 mg of alitretinoin.
- The other ingredients are ethanol, macrogol 400, hydroxypropylcellulose, and butylhydroxytoluene.

What Panretin looks like and contents of the pack
Panretin is a clear yellow gel. It is supplied in a multi-use 60 g epoxy-lined aluminium tube.
Each carton contains one tube of gel.

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Manufacturer
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For any information about this medicine please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Annex IV

Scientific conclusions

Scientific conclusions

On 7 July 2016 the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to review the routine risk minimisation measures in place for the oral and topical retinoids to ensure the available data and the risks associated with the adverse teratogenic effects and neuropsychiatric disorders are accurately and consistently addressed within the product information where appropriate and justified by data. Furthermore, the PRAC was requested to review any additional risk minimisation measures to ensure that these are optimal in terms of provision of information and delivery of effective risk management that is subject to appropriate monitoring. The PRAC was requested to assess the impact of the above concerns on the benefit-risk balance of retinoid-containing medicinal products and issue a recommendation on whether the products should be maintained, varied, suspended or revoked.

After reviewing all the available data to address the concerns discussed, the PRAC adopted a recommendation on 8 February 2018 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

The PRAC reviewed all available data from pre-clinical studies, pharmacovigilance data, published literature and spontaneous reports on the risks associated with the adverse teratogenic effects and neuropsychiatric disorders of oral and topical retinoids. In addition, the views of patients and healthcare professionals regarding communication, awareness and understanding of the risks of retinoids during pregnancy and in women of childbearing potential were taken into account in the recommendation along with their views on options for improving risk communication.

The review confirms the already known teratogenic risks associated with the use of oral retinoids in pregnant women. The data suggest that the risk of adverse pregnancy outcomes is more strongly associated with the oral retinoids than the topical retinoids. The animal reproductive toxicity data for the oral retinoids demonstrate a typical pattern of retinoid embryopathy. The human data on congenital malformations after oral retinoid exposure show a significant risk of retinoid embryopathy (of up to 30% of fetuses exposed); furthermore it is known that approximately one-third of pregnant patients exposed to oral retinoids during pregnancy will have spontaneous abortions. Pregnancy is an absolute contraindication for all oral retinoids in the EU.

The PRAC noted that despite the introduction of pregnancy prevention measures, including pregnancy prevention programmes (PPPs), cases of pregnancy during treatment with oral retinoid continue to be reported in the EU.

Compliance with the PPP is crucial to a positive benefit/risk balance for these products; therefore, the adequacy of the pregnancy prevention measures, including PPPs, for the oral retinoids acitretin, alitretinoin and isotretinoin has been reviewed to ensure that the available materials effectively encourage contraception use, regular pregnancy testing and shared responsibility between patients, doctors and pharmacists in adhering to recommendations, and that this is communicated consistently and effectively for all products. Furthermore, specific studies to measure effectiveness of the agreed changes to the PPP have been imposed on the marketing authorisation holders as an outcome of the referral.

In this respect, the PRAC recommended amendments to the product information, including harmonising the warnings and precautions of use for the oral retinoids acitretin, alitretinoin and isotretinoin to reflect the teratogenic risk associated with their use and communication to healthcare professionals through a direct healthcare professional communication. In addition, the PRAC recommended changes to the educational materials for the oral retinoids (acitretin, alitretinoin and isotretinoin) to ensure healthcare professionals and patients are informed about the risks associated

with oral retinoids (acitretin, alitretinoin and isotretinoin) in pregnant women and women of child-bearing potential and on the measures necessary to minimise the risk. These include a patient reminder card, physician checklist/acknowledgement form and pharmacist checklist ensuring the understanding and the awareness of prescribers and patients on the risks. The PRAC has also recommended that educational materials be distributed via electronic channels such as QR codes, and websites to make better use of the existing technology bearing in mind the young patient population using these products.

The PRAC acknowledged that the implementation of the following elements of the PPP need to be considered and agreed at national level to account for the different healthcare systems in the EU:

- The implementation of the 7-day prescription validity rule, in order not to impact on existing national legislation where 7 days validity exists;
- Patient signature of the physician checklist/acknowledgement form;
- Dissemination of the patient reminder card;
- Pharmacist checklist;
- Inclusion of appointment table in the patient reminder card;
- The option of a pictogram/symbol to accompany the box warning wording and to be included in the visual reminder on the outer package to warn patients about the harm to unborn baby and the need for effective contraception when using the medicinal product.

PRAC considered that given the oncological indications of oral tretinoin and oral bexarotene, further risk minimisation measures (RMMs) for these products regarding teratogenic effects, such as strengthening the product information (PI) and additional risk minimisation measures (aRMMs) would not provide an added value given the specialist management, the population at risk and the nature of the illness.

The PRAC noted the systemic exposure is negligible following topical application of retinoids and that this does not appear to be affected to a clinically significant degree by the severity or extent of skin disease. Studies that examine the effects of human pregnancy on systemic absorption of topical retinoids are also lacking. However, there was a consensus that several other factors may contribute to an increased systemic exposure and therefore the risk cannot be excluded.

Given that humans are the most sensitive species with respect to retinoid toxicity and considering the limitations of the available data with respect to understanding the systemic absorption and also the possible risks, the PRAC, considers that it is appropriate to take a very precautious approach. The indications for the topical retinoids are non-life-threatening and there is no absolute clinical need for the treatment during pregnancy and pregnancy should be excluded before prescribing. The PRAC thereby concludes that the benefit-risk balance of topical retinoids in pregnancy is not favourable, and therefore recommends that use of topical retinoids should be contraindicated during pregnancy and in women planning a pregnancy.

The PRAC recognizes that the available data in relation to oral retinoids and the occurrence of neuropsychiatric disorders have a number of important limitations that preclude the establishment of a clear causal association. Nevertheless, the PRAC considers that the data from patients presented in case series, spontaneous case reports and individual patients' experiences are considered to be very important. Although the underlying risk of psychiatric disorders within the patient populations can be significant, it is advisable that patients taking oral retinoids are warned about the potential risk of psychiatric reactions and the signs and symptoms to look out for. Therefore, the PRAC agrees that all oral retinoids should contain a warning about the potential risk of neuropsychiatric disorders in line with some key principles. The data support that for isotretinoin and alitretinoin the information in

section 4.4 and 4.8, of the SmPC, should be in line with the agreed outcome of the 2003 Art 30 referral for isotretinoin.

The PRAC further noted the extremely limited data relating to neuropsychiatric reactions after topical administration of retinoids. Given this and the negligible systemic exposure following topical no further risk minimization activities are deemed necessary.

Overall, the PRAC concludes that the benefit-risk balance of medicinal products containing retinoids remains favourable, but that marketing authorisation(s) should be varied for both the oral and topical retinoids to ensure risks associated with the adverse teratogenic effects and neuropsychiatric disorders are accurately and consistently addressed, as appropriate.

Grounds for PRAC recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for retinoid-containing medicinal products.
- The PRAC considered the totality of the data submitted, including responses from the marketing authorisation holders with regard to the consistency and effectiveness of existing routine and additional risk minimisation measures for oral and topical retinoids-containing medicinal products in relation to teratogenic effects and neuropsychiatric disorders. In addition, the PRAC considered the views of patients and healthcare professionals in relation to their understanding and the awareness of the teratogenic risk associated with the use of retinoid-containing medicines.
- With regards to the teratogenic risk, the PRAC confirmed that all oral retinoids (acitretin, alitretinoin, bexarotene, isotretinoin and tretinoin) are highly teratogenic and therefore must continue to be contraindicated during pregnancy or in women of child bearing potential unless they are using effective contraception. Given the indications and patients populations that use acitretin, alitretinoin and isotretinoin, it was considered that any use of these oral retinoids in female patients at risk of pregnancy must be in accordance with the conditions of a pregnancy prevention programme (PPP). For tretinoin and bexarotene, it was considered that in light of the oncological indications, specialist management in a hospital setting and population at risk that existing risk minimisation was appropriate and proportionate.
- The PRAC also concluded that there was a need to further harmonise and streamline the measures in the PPP including associated educational materials for the oral retinoids acitretin, alitretinoin and isotretinoin to ensure these are optimal to support discussions between patients and healthcare professionals on the risks and the associated risk minimisation measures.
- The PRAC further considered that for the oral retinoids acitretin, alitretinoin and isotretinoin a drug utilisation study with a complementary survey should be conducted to assess the effectiveness of the proposed updated risk minimisation measures.
- A direct healthcare professional communication (DHPC) was also considered appropriate for all oral and topical retinoids.
- With regards to the teratogenic risk of topical retinoids (adapalene, alitretinoin, isotretinoin, tretinoin and tazarotene), the PRAC concluded that the data available show that after topical application, systemic exposure is expected to be negligible and unlikely to result in adverse fetal outcomes. However, given that humans are the most sensitive species to retinoid embryopathy and that several other factors may contribute to an increased systemic exposure, such as excessive use and damaged skin barrier, the PRAC agreed that the teratogenic risk cannot be completely excluded. The PRAC therefore recommended that the use of topical retinoids should be

contraindicated during pregnancy and in women planning a pregnancy given the non-life threatening nature of the indications.

- With regards to neuropsychiatric disorders, the PRAC noted the limitations of the available data and considered that a clear causal relationship could not be established with the oral retinoids. However, taking into account the target patient population, the PRAC recognised the possible underlying risk of psychiatric disorders, and therefore recommended some changes to the product information such as warnings and precautions and so that the current level of available evidence is appropriately reflected.
- Furthermore, the PRAC noted the extremely limited data relating to neuropsychiatric reactions after topical administration of retinoids. Given this and the negligible systemic exposure following topical use, the PRAC considered that no further risk minimization activities are deemed necessary.

In view of the above, the PRAC considers that the benefit-risk balance of retinoid-containing medicinal products remains favourable subject to the agreed amendments to the product information and risk management plan, the conditions to the marketing authorisations and the related communication.

The PRAC, as a consequence, recommends the variation to the terms of the marketing authorisations for retinoid-containing medicinal products.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

The CHMP clarified that the communication plan should be modified to say ‘healthcare professionals who may be involved in the management of patients treated with retinoids’.

Overall conclusion

The CHMP, as a consequence, considers that the benefit-risk balance of retinoid-containing medicinal products remains favourable subject to the agreed amendments to the product information and risk management plan, the conditions to the marketing authorisations and the related communication.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for retinoid-containing medicinal products.