European Medicines Agency

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Product name: **Aldara**
Procedure No. **EMEA/H/179/II/26**

SCIENTIFIC DISCUSSION

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SCIENTIFIC DISCUSSION

1 Introduction

The Marketing Authorisation Holder (MAH), received the Centralised Marketing Authorisation on 18 September 1998 for Aldara (imiquimod) 5% cream. Imiquimod is indicated for the topical treatment of external genital and perianal warts (condylomata acuminata) in adult patients. In July 2004, the indication for small superficial basal cell carcinomas was approved.

The proposed amendments relate to an update of the SPC and consequential changes to the PL of Aldara 5% cream, to extend the therapeutic indication to include the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs) on the face or scalp in adult patients.

The proposed posology is one or two courses of imiquimod applied 3x/week for 4 weeks. The MAH received CHMP scientific advice in August 2000. A previous submission which sought an extension for the same therapeutic indication but with a longer treatment duration (3x/week for 16 weeks) was withdrawn by the MAH in March 2004 as major objections had been identified by the CHMP.

New data are available from one pharmacology study, four short-term trials, three long-term trials and six published studies.

Imiquimod belongs to the class of imidazoquinolinamines. Imiquimod is an immune response modifier that triggers toll-like receptors (TLR) on antigen-presenting cells such as monocytes/ macrophages and dendritic cells. Activation of TLR-7 results in increased transcription of cytokines, important in the innate immune responses, and by stimulating trafficking of dendritic cells to the regional lymph nodes, enhances the adaptive cell-mediated immune response in a manner consistent with a T-helper type 1 cell-mediated immunity.

1.1 Proposed new indication

Imiquimod cream is indicated for the topical treatment of …. clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs) on the face or scalp, in adult patients.

1.2 Proposed posology and method of administration

The application frequency for imiquimod cream is different for each indication.

Posology
"Actinic keratosis in adults: Apply imiquimod cream 3 times per week (example: Monday, Wednesday and Friday) prior to normal sleeping hours, and leave on the skin for approximately 8 hours. Continue imiquimod cream treatment for 4 weeks. After a 4-week treatment-free period the physician should assess the treated area to determine clearance of AKs. If any AKs persist in the treatment area, apply imiquimod cream 3 times per week for an additional 4 weeks (for a maximum total treatment duration of 8 weeks).

If you miss a dose, apply the cream as soon as you remember and then continue with your regular schedule. Do not apply the cream more than once in any day."

Method of administration
"Before applying imiquimod cream, patients should wash the treatment area with mild soap and water and dry thoroughly. Sufficient cream should be applied to cover the treatment area. The cream should be rubbed into the treatment area until the cream vanishes. The cream should be applied prior to normal sleeping hours and remain on the skin for approximately 8 hours. During this period, showering and bathing should be avoided. After this period it is essential that imiquimod cream is removed with mild soap and water. Sachets should not be re-used once opened. Hands should be washed carefully before and after application of cream. Clearance of AKs should be assessed at 4-8 weeks following each treatment period. A rest period of several days may be taken (see section 4.4) if

the local skin reaction to imiquimod cream causes excessive discomfort to the patient, or if infection is observed at the treatment site. In this latter case, appropriate other measures should be taken."

1.3 Problem statement: Actinic Keratosis

Actinic keratoses are common sun-induced precancerous lesions confined to the epidermis. Prevalence increases with advancing age. The majority (approximately 60%) of lesions are located on the upper limbs (Salasche S, J Am Acad Dermatol 2000; 42:S4-7). There are five clinical types: erythematous (desquamative-keratotic), keratotic papular, verrucous or papillomatous, pigmented and cutaneous horn. The vast majority of lesions are asymptomatic. Actinic keratoses may sometimes be associated with mild local irritation and pruritus and may be undesirable to the patient because of the cosmetic appearance. Lesions may regress spontaneously, with annual regression rates of approximately 25% (Marks R et al, Br J Dermatol, 1986, 115,649-655). On the other hand, actinic keratoses may progress to squamous cell carcinoma with a potential to metastasize estimated at around 3-6%. The chance of any given lesion developing into a squamous cell carcinoma is unknown. Relative risks depend on factors related to the lesion itself (e.g. thickness) as well as individual patient characteristics. Patients with actinic keratoses at thermal injuries and large scars, with immunosuppression, human papilloma virus infection and lesions on mucosal surfaces have an increased risk of malignant transformation (Butani A et al, Clin Plastic Surg 32(2005)223-235). The primary rationale of treating actinic keratosis is the prevention of progression to squamous cell carcinoma.

Pathogenesis of Actinic Keratosis

Risk factors for AKs include fair skin that burns easily and tans poorly, increasing age, male gender, reduced immune response after solid organ transplantation, and HPV infection. The primary pathogenesis of AKs and SCC stems from the effects of chronic UV damage to the keratinocyte. The energy from UVR can induce dimerisation between adjacent deoxyribonucleic acid (DNA) pyrimidine bases, resulting in mutations in the DNA. Mutations in the regulatory tumour suppressor gene p53 can be particularly harmful. Programmed cell death of genetically altered keratinocytes (apoptosis) is a p53-dependent process that guards against early neoplastic cell survival. If both copies of the regulatory tumour suppressor gene p53 have mutated as a result of UVR, its protective role is lost. This leads to preservation of transformed keratinocytes that can mutate and develop into AKs. In addition to inducing cell mutations, UVR also appears to attenuate the recognition of malignant cells by cell-mediated immunity (CMI). By weakening the immune response, chronic UVR induces a reduced antitumour immune defence. This suppression has been shown to play a significant role in development of SCC and may be a factor in the transformation rate of AKs into SCCs.

Currently available therapies for Actinic Keratosis

The most common current therapies for AKs are:

- 5-fluorouracil (5-FU) is a **c**ytotoxic agent, administered topically
- Topical Photodynamic Therapy (PDT) consists of an application of photosensitiser (eg, methyl aminolevulinate), which preferentially localises in tumor tissue with subsequent illumination with appropriate light to produce reactive oxygen intermediates
- Diclofenac 3% in 2.5% hyaluronan gel is a cyclooxigenase inhibitor
- Curettage and electrodesiccation **s**crape lesion away, then achieve hemostasis with electrical current
- Cryotherapy is a method which uses liquid nitrogen to freeze and destroy tissue.

AKs frequently involve a large part of the exposed skin with multiple lesions. Cryotherapy is not an easily acceptable option when numerous or big lesions must be treated.

2 Nonclinical aspects

Non-clinical data are available from an SKH-1 hairless mouse model of UV irradiation induced actinic keratosis (Study Imiquimod-020702-001). The results of this trial were previously submitted and assessed.

The objective of this study was to determine whether imiquimod could reduce actinic keratosis lesions induced in the SKH-1 mouse model by low levels of UV irradiation. 0.6%, 1% and 3% imiquimod cream were topically applied three times a week for 3-4 weeks. Actinic keratosis lesions were reduced by 24%, 27% and 59%, respectively. 5% imiquimod cream was not tolerated and 0.1% had no effect. Increases in IL-12, interferon, monocyte chemoattractant protein-1 (MCP-1) and TNFα were observed following 1% and 5% imiquimod application. The observations are consistent with the hypothesis that stimulated immune responses may contribute to inhibition and resolution of actinic keratosis lesions. The model suggests imiquimod may have potential in the treatment of actinic keratosis.

3 Clinical aspects

3.1 Clinical pharmacology

The clinical development programme for actinic keratosis includes seven previously submitted and assessed phase I trials and a new phase II study (1467-IMIQ). From these, two studies have explored the mechanism of action of imiquimod on AKs: 1467-IMIQ evaluated 3x/week dosing for 4 weeks, and 1428-IMIQ evaluated 3x/week dosing for 16 weeks.

Table 1: List of clinical pharmacology studies

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1244-IMIQ	Phase I, vehicle-controlled, photocontact allergenicity study evaluating imiquimod 5% cream in 2 cohorts of 60 healthy subjects each; doses applied to the lower mid-back.	Imiquimod and vehicle cream (200 µl) 2x/wk for 3 wks followed by a single challenge dose (applied to 2 sites) 10-14 days post last dose (7)	No detectable photocontact allergenicity potential seen. Photoirritation was reported by 42% (25/60) of subjects during the induction phase.
1249-IMIQ	Phase I, open-label, vehicle-controlled, 4-day safety study to assess the phototoxic potential of imiquimod 5% cream in 21 healthy subjects; doses applied to lower midback.	Imiquimod and vehicle cream (200 µl) Single dose in duplicate / 24 hours (2)	No detectable phototoxic potential was observed or reported for either imiquimod or vehicle.
1270-IMIQ	Phase I, open-label, vehicle-controlled, 21-day cumulative irritation study in 40 healthy subjects; doses applied to forearm (sun-damaged area) and upper arm (normal area).	Imiquimod and vehicle cream (200 µl)[a]: 1x/d (in duplicate) for 21 days (42)	Imiquimod was less irritating to sun-damaged skin than normal skin. There was no difference between imiquimod and vehicle.

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1281-IMIQ	Phase I, randomized, single-blinded, vehicle-controlled study in 2 cohorts of 22 subjects each to assess photoirritation: sunburn cell induction and pyrimidine dimer formation upon exposure to UVR	Imiquimod and vehicle cream (100 µl): 1x/d (Mon-Sat) for 3 weeks, then 1x/d (Mon-Th) for 1 week (22)	Sunburn cell and pyrimidine dimer analyses showed that imiquimod did not increase the response of white skin to UVR exposure.
1359-IMIQ	Phase I, randomized, double-blind, vehicle-controlled study in 24 healthy volunteers; doses applied to arm	Imiquimod and vehicle cream (250 mg): 1x/d, 3x/week for 4 weeks (12), or 1x/d, 7x/week for 4 weeks (28)	There were minimal histological changes noted in healthy skin during the conduct of this study. No trends were seen between imiquimod and vehicle treated sites or any dose frequency related trends between the imiquimod treatment groups.
1402-IMIQ	Phase I open-label safety study in 58 subjects with AK lesions; imiquimod 5% cream was applied to either face, scalp, or hands/arms	Imiquimod cream (250 mg) : Face group: 1 sachet/dose 1x/d, 3x/wk for 16 wks (48) Scalp group: 2 sachets/dose 1x/d, 3x/wk for 16 wks (48) Hands/arms group: 6 sachets/dose 1x/d, 3x/wk for 16 wks (48)	Systemic imiquimod serum concentrations were generally low, providing a large safety margin. Using the calculated area-under-the-curve values, safety margins for the three topical doses were found to be 303, 128, and 11, respectively.
1428-IMIQ	Phase I, randomized, double-blind, parallel group, vehicle-controlled study in 18 subjects with AK. 2:1 ratio of imiquimod to vehicle.	Imiquimod or vehicle cream (250 mg) : 1x/d, 3d/wk for 16 wks or until clear, whichever occurred first (up to 48)	The imiquimod group showed statistically significant increases from baseline to week 2 levels for CD3, CD4, CD8, CD11c, CD86/CD11c double stain, CD68, HLA-DR, and TUNEL. No significant correlations between clearance and week 2 biomarker levels were seen for the imiquimod group.

Study 1467-IMIQ

This phase II study was performed to assess apoptosis by examining the gene expression profiles of actinic keratosis lesions.

Seventeen male subjects with 7-13 actinic keratosis lesions on the scalp were randomised to either imiquimod 5% cream or vehicle cream (3:1 randomisation) once daily 3 times per week for 4 weeks. Pre-treatment biopsies were taken from AKs lesions, non-lesioned sun-exposed and non-lesioned sun-unexposed areas. Biopsies of different lesions were taken at study weeks 1, 2, and 4, and four weeks post-treatment. Gene expression in shaved biopsy samples was studied qualitatively by gene chip technology and quantitatively by quantitative reverse transcriptase polymerase chain reaction. Clinical efficacy was not evaluated in this study.

Observed changes were increased expression of several Toll-like receptor genes, induction of antiviral and antitumor IFN-inducible genes, increased expression of proapoptotic genes and of genes that indicate infiltration and activation of immune cells such as natural killer cells and plasmacytoid dendritic cells, increased induction of genes that suggest the up-regulation of the adaptive immune system and reversal of some tumour immune evasion mechanisms. However, the study presents some limitations that make the interpretation of the results awkward and do not allow definite conclusions to be drawn about genetic expression during the course of the disease and treatment. Moreover, efficacy was not evaluated in this study so no correlation can be done with these biomarkers and efficacy.

3.2 Clinical efficacy

The clinical development programme for actinic keratosis includes seven phase I, five phase II and eleven phase III (nine short-term studies and two long-term) studies. A further long-term study was submitted during the evaluation of this variation.
A tabular overview of these trials is presented in the Table 2.

Table 2: List of clinical phase II and phase III studies

Summary of phase II studies

3x/week for 4 weeks, one or two courses - Phase II Study

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1459-IMIQ	Phase II, double-blind, vehicle-controlled pilot study of 82 adult subjects with AK. Imiquimod: vehicle (1:1)	Imiquimod or vehicle cream (250 mg) 1x/d, 3x/wk for 1 or 2 cycles of 4 weeks each (12 or 24)	Complete clearance overall, imiquimod 46% (18/39), vehicle 9% (4/43). Complete clearance for cycle 1: imiquimod 41% (16/39), vehicle 5% (3/43). 10% (4/39) of imiquimod subjects, and 0/43 vehicle subjects reported application site reactions. No SAEs, no deaths

Other Phase II Study

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1176-IMIQ	Phase II, double-blind, vehicle-controlled study in 41 adults with AK. Imiquimod to vehicle (2:1)	Imiquimod or vehicle cream (100 µl)[b]: 2x/d, 7x/wk for up to 16 wks (224) 1x/day, 7x/wk for up to 16 wks (112) 1x/d, 3x/wk for up to 16 wks (48) 1x/d, 1x/wk for up to 16 wks (16)	Complete clearance of all 3 AK lesions in the treatment period in 37% (10/27) of imiquimod subjects, 7% (1/14) of vehicle subjects 30% of imiquimod subjects and 14% of vehicle subjects reported application site reactions.
1252-IMIQ	Phase II, open-label study in 16 adult subjects with Bowen's disease	Imiquimod cream (250 mg) 1x/d, 7x/wk for 16 wks (112)	Complete clearance ITT = 88%, 14/16, (PP = 93%, 14/15). 3 SAEs occurred after treatment ended; none was related to study cream
1381-IMIQ	Phase II, double-blind, vehicle-controlled study of 149 adult subjects with AK. Imiquimod: vehicle (4:1)	Imiquimod or vehicle cream (250 mg) 1x/d, 2x/wk for 8 wks (16) 1x/d, 3x/wk for 8 wks (24) 1x/d, 5x/wk for 8 wks (40) 1x/d, 7x/wk for 8 wks (56)	No statistically significant difference between any imiquimod dose group vs. vehicle for complete clearance Seven SAEs and 1 death occurred. Mild lymphopenia, possibly/probably related to study drug was seen in 16 subjects (15 imiquimod; 1 vehicle)

3x/week for 4 weeks, one or two courses - Phase II Study

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1467-IMIQ	Phase II double-blind, vehicle-controlled study to evaluate cellular and molecular events in 17 subjects with biopsy confirmed AK. Imiquimod or vehicle (3:1).	Imiquimod or vehicle cream (250 mg) 1x/d, 3x/wk for 4 weeks (12)	Efficacy was not evaluated in this study No specific AE was reported by more than 1 subject. No SAEs and no deaths were reported.

Summary of Phase III studies

3x/week for 4 weeks, one or two courses - Phase III Studies

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1473-IMIQ	Double-blind, parallel group, vehicle-controlled study in 246 adult subjects with AK. Ratio of vehicle to imiquimod 1:1.	Imiquimod or vehicle cream (250 mg) 1x/d, 3x/wk for 1 or 2 COT of 4 weeks each (12 or 24)	By clinical assessment: Imiquimod Overall: 53.7% (66/123) After Course One: 26.8% (33/123) Vehicle Overall: 14.6% (18/123) After Course One: 4.1% (5/123) 7 subjects (3 imiquimod, 4 vehicle) reported 8 SAEs, no deaths.
1487-IMIQ	Double-blind, parallel group, vehicle-controlled study in 259 adult subjects with AK. Ratio of vehicle to imiquimod 1:1.	Imiquimod or vehicle cream (250 mg) 1x/d, 3x/wk for 1 or 2 COT of 4 weeks each (12 or 24)	By clinical assessment: Imiquimod Overall: 55.0% (71/129) After Course One: 37.2% (48/129) Vehicle Overall: 2.3% (3/130) After Course One: 0.8% (1/130). 5 subjects (1 imiquimod, 4 vehicle) reported 10 SAE), 1 death (vehicle).
1511-IMIQ	Phase IIIb open-label study to assess the safety and efficacy of imiquimod applied once daily 3 days per week for the treatment of AK on the head in 829 subjects.	Imiquimod cream applied 1x/d 3x/wk for 1 or 2 COT of 4 wks each (up to 2 sachets per dose) (12 or 24 doses)	By clinical assessment: Overall: 68.9% (571/829) After Course One: 40.5% (336/829) 26 subjects reported 40 SAEs, 2 deaths

Phase III 3x/week for 4 weeks, one or two courses Long-Term Follow-up Study

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1518-IMIQ	Treatment-free follow-up study to evaluate recurrence of AK after completion of the 1473-IMIQ study.	None	Results presented in the topic "Long-Term Follow-Up Studies"
1524-IMIQ	Treatment-free follow-up study to evaluate recurrence of AK after completion of the 1487-IMIQ study.	None	Results presented in the topic "Long-Term Follow-Up Studies"

Phase III 16-week Studies

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1444-IMIQ	Phase III double-blind, parallel group, vehicle-controlled study in 217 adult subjects with AK, 1:1 ratio of imiquimod to vehicle.	Imiquimod or vehicle cream (250 mg): 1x/d, 2x/wk for 16 wks (32)	By clinical assessment: Imiquimod: 49/107 (45.8%) Vehicle: 3/110 (2.7%) 10 subjects (5 imiquimod, 5 vehicle) reported 17 SAEs, no deaths.
1445-IMIQ	Phase III double-blind, parallel group, vehicle-controlled study in 241 adult subjects with AK, 1:1 ratio of imiquimod to vehicle.	Imiquimod or vehicle cream (250 mg): 1x/d, 3x/wk for 16 wks (48)	By clinical assessment: Imiquimod: 66/117 (56.4%) Vehicle: 10/124 (8.1%) 12 subjects (6 imiquimod, 6 vehicle), reported 30 SAEs, no deaths.
1446-IMIQ	Phase III double-blind, parallel group, vehicle-controlled study in 219 adult subjects with AK, 1:1 ratio of imiquimod top vehicle.	Imiquimod or vehicle cream (250 mg) 1x/d, 2x/wk for 16 wks (32)	By clinical assessment: Imiquimod: 48/108 (44.4%) Vehicle: 4/111 (3.6%) 8 subjects (5 imiquimod, 3 vehicle) reported 13 SAEs, 1 death (imiquimod).
1447-IMIQ	Phase III double-blind, parallel group, vehicle-controlled study in 251 adult subjects with AK, 1:1 ratio of imiquimod to vehicle.	Imiquimod or vehicle cream (250 mg): 1x/d, 3x/wk for 16 wks (48)	By clinical assessment: Imiquimod: 51/125 (40.8%) Vehicle: 8/126 (6.3%) 8 subjects (6 imiquimod, 2 vehicle) reported 12 SAEs, no deaths.[b]
1450-IMIQ	Phase III double-blind, parallel group, vehicle-controlled study in 286 adult subjects with AK, 1:1 ratio of imiquimod to vehicle.	Imiquimod or vehicle cream (250 mg): 1x/d, 3x/wk for 16 wks (48)	By histological/ clinical assessment: Imiquimod: 84/147 (57.1%) Vehicle: 3/139 (2.2%)

Long Term Follow-up to the 16-week Phase III Studies

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1486-IMIQ	Phase III treatment free follow-up study to evaluate AK recurrence rates in 146 subjects 1 year or more after completion of 1444-IMIQ, 1445-IMIQ, 1446-IMIQ, and 1447-IMIQ studies.	NA	AK Recurrence Rate (subject-based): Imiquimod 3x/wk: 19/77 (24.7%) 2x/wk: 23/54 (42.6%) Vehicle 3x/wk: 6/12 (50.0%) 2x/wk: 1/3 (33.3%) AK Recurrence Rate (lesion-based) Imiquimod 3x/wk: 27/424 (6.4%) 2x/wk: 33/296 (11.1%) Vehicle: 3x/wk: 3/15 (20.0%) 2x/wk: 11/69 (15.9%) No SAEs, no deaths.

Other Phase III Studies

Study	Study Design and Population	Dose frequency/ duration of treatment	Results
1436-IMIQ	Multicentre, randomized, double-blind, parallel study to assess the safety and efficacy of imiquimod in the treatment of AK in 65 subjects; ratio of imiquimod to vehicle (2:1).	Imiquimod or vehicle cream (250 mg): 1x/d 3x/wk, with the option to decrease to 2x/wk at the discretion of the investigator, for 12 wks (24-36)	By histological/ clinical assessment: Imiquimod: 10/41 (24.4%) Vehicle: 0/21 (0.0%) 4 subjects (3 imiquimod, 1 vehicle) reported 5 SAEs 1 death (1 imiquimod).

Main studies

Pivotal short-term studies: Study 1473-IMIQ and Study 1487-IMIQ

Two new pivotal studies have been submitted:

- Study **1473-IMIQ** was conducted at 13 centres in the US between October 2003 and July 2004.
- Study **1487-IMIQ** was conducted at 20 centres in Europe between December 2003 and November 2004.

These studies were essentially of identical design, with the exception that the European study included biopsies.

Study participants, target lesions

Subjects were required to have 4 to 8 (study 1487: 5-9) clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AKs lesions located within a contiguous 25cm^2 treatment area (balding scalp or face, but not both).

Identification of actinic keratosis was based on clinical evaluation by a qualified dermatologist and in study 1487 confirmed by biopsy. One representative lesion was biopsied before therapy, and another lesion was identified to be biopsied 8 weeks post-treatment.

Biopsy specimens were assessed by two independent blinded dermatopathologists in a central laboratory. In cases of disagreement, a consensus diagnosis was reached.

Treatments

Patients were randomised to either imiquimod 5% cream or vehicle three times a week, applied before going to bed, for one or two courses of four weeks each, with four weeks between courses.

Primary endpoints:

1) To compare imiquimod and vehicle cream with respect to the complete clearance rate after Course One
2) To compare imiquimod and vehicle with respect to the overall complete clearance rate.

Clearance was assessed both clinically (4 and 8 weeks post-treatment) and histologically (8 weeks post treatment) in study 1487. In study 1473, only clinical assessment was performed (4 weeks post-treatment for patients who had only one course, and 4 or 8 weeks post-treatment for subjects who had had two courses).
Complete clearance was defined as no clinical (and histological) evidence of AKs in the treatment area at the above time points.

Secondary endpoints:
The secondary endpoints included the following:

- Partial clearance rate, defined as the proportion of subjects at their last study visit who had at least 75% reduction in the number of AKs lesions counted at baseline in the treatment area. If the post-treatment biopsy was positive for AKs or was not done, this lesion was considered present in the count of AKs lesions;
- Partial clearance rate after Course One, defined as the proportion of subjects at the Course One 4-week post-treatment visit with at least 75% reduction in the number of AKs lesions counted at baseline in the treatment area)
- Clearance rate of individual AKs lesions. The reduction in individual AKs lesions from baseline was summarised.

Results
246 patients were included in study 1473, and 259 in study 1487.
In both studies the majority of patients were of male gender, had either Fitzpatrick skin type II or III and had had previous AK treatments. The median number of baseline lesions was 6, except for the vehicle group in 1487-IMIQ who had a median of 7. All patients but one were “white”. The median age was 65 to 73 years.

Treatment of actinic keratosis with imiquimod provided significant benefit when compared to treatment with vehicle at 4 to 8 weeks post-treatment. A statistically significant difference was seen for all primary and secondary efficacy outcomes after one or two courses of treatment. Tables 3a and 3b below summarise the results for primary and secondary endpoints.

Table 3a: Efficacy results of pivotal short-term studies 1473 and 1487 - Primary endpoints

Study	**Imiquimod**	**Vehicle**	**P-Value**
PRIMARY ENDPOINTS			
Overall Complete Clearance			
1473-IMIQ	53.7% (66/123)	14.6% (18/123)	<0.0001
1487-IMIQ	55.0% (71/129)	2.3% (3/130)	<0.0001
Complete Clearance at End of Course One			
1473-IMIQ	26.8% (33/123)	4.1% (5/123)	<0.0001
1487-IMIQ	37.2% (48/129)	0.8% (1/130)	<0.0001

Table 3b: Efficacy results of pivotal short-term studies 1473 and 148 7- Secondary endpoints

Study	Imiquimod	Vehicle	P-Value
SECONDARY ENDPOINTS			
Overall Partial Clearance			
1473-IMIQ	61.0% (75/123)	25.2% (31/123)	<0.0001
1487-IMIQ	65.9% (85/129)	3.8% (5/130)	<0.0001
Partial Clearance at End of Course One			
1473-IMIQ	36.6% (45/123)	5.7% (7/123)	<0.0001
1487-IMIQ	46.5% (60/129)	0.8% (1/130)	<0.0001
Overall Clearance of Individual AK Lesions			
1473-IMIQ	74.4% (564/758)	37.6% (268/713)	--
1487-IMIQ	75.7% (674/855)	18.9% (161/852)	--
Clearance of Individual AK Lesions at End of Course One			
1473-IMIQ	56.3% (427/758)	20.3% (145/713)	--
1487-IMIQ	61.1% (522/855)	11.3% (96/852)	--

The MAH has provided clearance rates (active minus placebo) for the combined COT trials. The difference in complete clearance rates between imiquimod and placebo for the combined COT trials was 46.1% (39.0%, 53.1%).

Table 4: Clearance Rates (Active minus Placebo) for Combined COT studies

Study	Complete Clearance Imiquimod %	Complete Clearance Vehicle %	Complete Clearance Active-Vehicle [95% CI]
Individual COT Studies			
1473-IMIQ	53.7%	14.6%	39.1% [28.2%, 49.8%]
1487-IMIQ	55.0%	2.3%	52.7% [43.8%, 61.7%]
Combined COT Studies	**54.4%**	**8.5%**	**46.1% [39.0%, 53.1%]**

Abbreviations: CI=confidence interval, COT=course of treatment

The MAH has presented comparisons with published clearance rates for licensed topical treatments of AK. The CHMP agrees that the short-term lesion clearance rates appear to be in the same order of magnitude for imiquimod and other topical treatments but the comparison is problematic due to a number of factors such as comparison with treatments not licensed in the EU, open-label trial design, location and size of target lesions, timings of assessment, etc. Robust comparative data should be submitted as a postmarketing commitment.

Long-Term Follow-Up Studies

The MAH has submitted results from three studies providing long-term data. These trials evaluated recurrence and local skin reactions and skin quality following treatment with either 1 or 2 four-week courses of imiquimod 3x/week (1518-IMIQ: follow-up of study 1473-IMIQ, 1524-IMIQ: follow-up of study 1487-IMIQ) or 16 weeks of continuous treatment with imiquimod 2x/week or 3 times /week (1486-IMIQ: follow-up of studies 1444, 1445, 1446 and 1447-IMIQ).

Study 1518 and 1524 provide data relevant to the proposed dosing schedule. The duration of the follow-up studies is limited to one year. Trial 1486-IMIQ is summarised in table 2.

1518-IMIQ and 1524-IMIQ

Trials 1518-IMIQ and 1524-IMIQ were both single-visit studies providing observational follow-up data on subjects who had completely cleared their AKs in the pivotal short-term trials at any of the post-treatment visits in trials 1473-IMIQ and 1487-IMIQ.

The primary endpoint was the patient based recurrence rate. Subjects with at least 1 AKs lesion in the treatment area at the follow-up visit or who had received interventions related to AKs or SCC in the treatment area were considered to have a recurrence.
Assessment of the previous treatment area for recurrences, suspicious lesions, local skin reactions and skin quality was performed by a qualified dermatologist. Lesions suspicious for malignancy were to be removed and specimens sent to a central dermatopathologist for confirmation of clinical diagnosis. Information was collected on any dermatologist-confirmed diagnoses and therapies in the treatment area since the completion of the previous studies.
Table 5 summarises recurrence rates as reported from the three 'long-term' trials.

Table 5: Recurrence rates

		PATIENT-BASED RECURRENCE RATE %		**LESION-BASED RECURRENCE RATE %**	
		Imiquimod	**vehicle**	**Imiquimod**	**vehicle**
3x/wk for 4 weeks, one or two treatment courses					
1518-IMIQ		39% (23/59)	57% (8/14)	8.7% (27/310)	9.7% (6/62)
1524-IMIQ		17.4% (12/69)	0% (0/3)	3.3% (14/427)	0% (0/18)
2x/wk for 16 weeks					
1486-IMIQ		42.6% (23/54)	33.3% (1/3)	11.1% (33/296)	20.0% (3/15)
3x/wk for 16 weeks					
1486-IMIQ		24.7% (19/77)	50.0% (6/12)	6.4% (27/424)	15.9% (11/69)

Calculated across trials 1518- and 1524-IMIQ the lesion recurrence rate for imiquimod is 5.6% (41/737) and the patient-based recurrence rate 27% (35/128). Corresponding recurrence rates for vehicle are 7.5% (6/80 lesions) are 47% (8/17 patients).
A comparison of data obtained from trials 1518- and 1524-IMIQ with those data cited in literature for other treatments is problematic due to factors such as different study design, treatment areas (e.g. head, extremities), and lengths of follow-up periods. Therefore a robust conclusion regarding comparative long-term efficacy cannot be drawn.
It is considered that the reported recurrence rates are within an acceptable range. The MAH has been requested to provide robust comparative data as a postmarketing commitment.

Progression to squamous cell carcinoma:
Data from three 'long-term' trials indicate that 1.15% (3/259) of imiquimod-patients and 0% (0/32) vehicle-patients had developed SCC within the follow-up period. A comparison of imiquimod versus vehicle rates is hampered by unequal group sizes.

Table 6: Patient based SCC rates

	Patient based SCC rates	
	Imiquimod	**Vehicle**
3x/wk for 4 weeks, one or two treatment courses		
1518-IMIQ	2/59	0/14
1524-IMIQ	0/69	0/3
2x/wk for 16 weeks		
1486-IMIQ	0/54	0/3
3x/wk for 16 weeks		
1486-IMIQ	1/77	0/12

The rate of progression on a *per-patient* basis at one year (1.15% for all studies, 1.6% for trials using the proposed posology only) is comparable to that presented in published literature using a mathematical model (Dodson 1991). Although the MAH has not submitted a calculation of rates of progression on a per-lesion basis, it would appear that at 0.2% this, too, is in the range reported in literature (Marks 1986, 1988). A comparison of imiquimod versus vehicle rates is hampered by unequal group sizes.

The comparison of progression rates for imiquimod to those reported in literature suffers from limitations such as different study design, different lengths of follow-up, etc.

Bibliographic evidence
The MAH has presented six published studies to provide further evidence for imiquimod in the treatment of actinic keratosis.

Discussion

The CHMP requested to restrict the indication to *immunocompetent* patients in *whom size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate*. This restriction was based on the conclusion that the proposed patient population is likely to be elderly and suffer from concomitant diseases (e.g. occult carcinoma with reduced haematologic reserve) that may make them more vulnerable to some of imiquimod's adverse effects, that the condition to be treated in itself is not malignant, that the established benefit is limited to clearing certain types of actinic keratosis lesions, that the benefit with regard to the prevention of progression to squamous cell carcinoma has not been established and that treatment options with a more favourable safety profile are available.

To avoid ambiguity in the product information a warning statement to exclude the treatment of AKs lesions with marked hyperkeratosis or hypertrophy such as seen in cutaneous horns was added to section 4.4.

A restriction to specialist use was also discussed. This was based on the concern about the low positive predictive value of the clinical diagnosis of AK (approximately 70%) even when diagnosis is made by a specialist, with the potential of misdiagnosing malignant lesions as AK. As any concern over significant discrepancies between clinical and histological diagnosis of the condition would be an issue relevant to any treatment for AK, it was considered that restriction to specialist use for imiquimod only would not be justified.

Application frequency and duration of treatment
Two trials demonstrated that imiquimod at the proposed posology is superior to placebo in clearing actinic keratosis lesions when assessed at 4 to 8 weeks post-treatment. Trials investigating longer treatment duration (16 weeks) did not demonstrate higher short-term clearance rates. A comparison of "long-term" (approximately one-year) follow-up data indicated that recurrence rates were higher when imiquimod was administered 2x/week for 16 weeks as compared to 3x/week. These data, taken together, were accepted as adequate justification for the proposed posology.

Concentration
The issue of whether a concentration of < 5% imiquimod would be effective and give fewer side-effects was discussed. In external genital warts trials, a 1% concentration revealed a lack of efficacy, indicating inadequate tissue concentration. Considering that actinic keratosis lesions are not less keratinized than external genital warts, the MAH concludes that the 5% concentration is also appropriate for adequate penetration in treating actinic keratosis. Since clinical efficacy has been demonstrated for the 5% cream for actinic keratosis, the extrapolation of concentration data from external genital warts to actinic keratosis was considered acceptable.

Short-term efficacy
The two pivotal short-term trials demonstrated that treatment of actinic keratosis provided significant short-term benefit when compared to vehicle. Direct comparative data to cryotherapy or licensed topical treatments (5-FU, diclofenac, methyl-5-aminolevulinate) are not available. Comparisons with data reported in literature suffer from several flaws and limitations, but indicate that short-term lesion clearance rates for imiquimod are within the same order of magnitude as reported for other topical treatments.

Long term efficacy – Recurrence rate
Calculated across trials 1518- and 1524-IMIQ the lesion recurrence rate for imiquimod is 5.6% (41/737) and the patient-based recurrence rate 27% (35/128). Corresponding recurrence rates for vehicle are 7.5% (6/80 lesions) are 47% (8/17 patients). CHMP considered these recurrence rates to be within an acceptable range for the observed period of time. Recurrence rates at 3 years have not been determined.
A comparison of data obtained from trials 1518- and 1524-IMIQ with those cited in literature for other topical treatments is problematic due to factors such as different study design, treatment areas and length of follow-up periods. Therefore a robust conclusion regarding comparative long-term efficacy could not be drawn.

Long term efficacy – Progression to squamous cell carcinoma
The initial submission included incomplete data from one follow-up trial assessing the proposed posology. The results indicated that 3.4% of patients had progressed to squamous cell carcinoma within one year. Calculated on the basis of the additional data submitted during the procedure, the rate of progression on a *per-patient* basis at one year (1.15% for all studies (1518-, 1524- and 1486-IMIQ), 1.6% for trials using the proposed posology only) is comparable to that presented in published literature based a mathematical model (Dodson 1991). Although the MAH has not submitted a calculation of rates of progression on a per-lesion basis, it would appear that at 0.2% this, too, is in the range reported in literature (Marks 1986).

Comparative efficacy - Comparator trial
Since actinic keratosis can progress to invasive squamous cell carcinoma, the CHMP had requested that the MAH provide 3-year follow-up data. Furthermore, the absence of a comparator trial was considered a concern since absence of comparative data hampers the evaluation of the benefit/risk for this indication. The MAH agrees to conduct a 3-year follow-up study as a postapproval commitment to investigate recurrence and progression rates and time to recurrence. CHMP Scientific Advice will be sought for the design of this trial.

3.3 Clinical safety

The MAH has provided an integrated safety review that takes into consideration the entirety of the available safety data: a) across all studies in the clinical development programme, b) across all studies using the proposed posology.

Extent of exposure
The safety review submitted by the MAH includes 23 studies[1] with 3243 patients. The Summary of Clinical Safety states that five studies are ongoing. Safety information for ongoing studies was reported up to 1 July 2005.

Adverse events
Eighteen (18) patients died in completed and ongoing studies, 14 on imiquimod, 3 on vehicle and 1 non-randomised patient. None of the deaths were considered related to imiquimod.

One hundred eighty two (182) serious adverse events (SAEs) were reported by 107 patients. 118 events were reported by 73 imiquimod subjects and 64 events were reported by 34 vehicle subjects.

[1] 1176, 1244, 1249, 1252 (*M. Bowen*), 1270, 1281, 1359, 1381, 1402, 1428, 1436, 1443, 1444, 1445, 1446, 1447 , 1450,1459, 1467, 1473, 1486, 1487, 1502, 1511, 1516, 1518, 1519, 1520, 1524-MIQ

None of the SAEs were considered related to study drug except one patient had a possible metastatic squamous cell carcinoma in an anatomical location outside the area treated with imiquimod that was considered as possibly related to study drug.

In the completed phase I - III studies, 77 patients on imiquimod and 15 vehicle-patients discontinued treatment due to adverse events. In the pivotal short-term studies 1473- and 1487-IMIQ, three imiquimod-patients and no vehicle-treated patient discontinued treatment due to local skin reactions.

In relation to non-serious adverse events in two of the three double-blind comparative studies assessing the proposed posology adverse events were reported in 56% of imiquimod-patients and 41.9% of vehicle-patients. Application site reactions, myalgia and fatigue were statistically significantly more common on imiquimod.

Application site reactions
A review of the two pivotal trials assessing the proposed posology demonstrated that application site reactions such as itching, burning, erythema, pain, inflammation, swelling were reported spontaneously as an adverse event by 22.2% of imiquimod-treated patients versus 5.1% on vehicle-treated patients. Local skin reactions were also assessed by the investigators in a prospectively defined manner at each visit. Erythema, oedema, vesicles, erosion/ulceration, weeping/exudate, flaking/scaling/dryness and scabbing/crusting were all reported very commonly (>1/10). Erythema was mostly moderate (51.2% imiquimod patients) to severe (23.8% imiquimod patients), the other reactions mostly mild to moderate. Local skin reactions were most intense at week 4 and were generally less intense in course two than course one. Severe erythema was the most commonly reported severe skin reaction.

(Auto)immune conditions
Recent Periodic Safety Update Reports (PSURs) have raised the concern that imiquimod may be associated with stimulation or exacerbation of (auto)immune conditions such as thrombocytopenia, rheumatoid arthritis, psoriasis, multiple sclerosis, Crohn's disease, thyroiditis and SLE, lichen sclerosus (PSUR no 9). Since there is a potentially plausible mechanism of action for this effect and some of the cases strongly suggested causality, a warning statement that imiquimod cream should be used with caution in patients with autoimmune conditions had been added to the SPC (via type II variation 27).

Alopecia
In the integrated safety review across the imiquimod studies in the AKs development program, 7/1214 (0.6%) imiquimod subjects reported alopecia as an adverse event compared to 0/981 (0%) vehicle subjects. Of the 7 events reported by imiquimod subjects, 5 were considered by the investigator to be related to study drug. To reflect this information the following text is introduced in Section 4.8: *"Clinical studies investigating the use of imiquimod for the treatment of actinic keratosis have detected a 0.4% (5/1214) frequency of alopecia at the treatment site or surrounding area. Postmarketing reports of alopecia occurring during the treatment of sBCC and EGW have been received."*

Serious skin reactions
A review of the MAH's safety databases identified 8 reports of serious skin reactions from clinical trials (67 trials including 9872 patients) and 19 reports from the post-marketing safety database. All cases identified from clinical trials were temporally associated with the use of imiquimod (n = 7) or vehicle (n = 1). For two cases of exanthema, the outcome was reported as persistent. The majority of spontaneously reported cases were reported by physicians. In one case erythema multiforme was confirmed by skin biopsy. In several cases there was a temporal association with imiquimod use. In several cases, the event abated after treatment was stopped.

A warning about serious skin reactions has been included in Section 4.8 of the SPC :*"Rare cases of remote site dermatologic drug reactions, including erythema multiforme, have been reported from clinical trials. Serious skin reactions reported from postmarketing experience include erythema multiforme, Stevens Johnson syndrome and cutaneous lupus erythematosus."*
Serious skin reactions are included in the Risk Management Plan as *identified* risks and Stevens Johnson syndrome as *potential* risk requiring further evaluation.

Laboratory findings

In the pivotal trials 1473-IMIQ and 1487-IMIQ, there was a statistically significant decrease in haemoglobin, white blood cell count, absolute neutrophil count, and platelet counts in the imiquimod group as compared with vehicle. This finding is already reflected in section 4.8 of the SPC as follows: "*Reductions in haemoglobin, white blood cell count, absolute neutrophils and platelets have been observed in clinical trials. These reductions are not considered to be clinically significant in patients with normal haematologic reserve. Patients with reduced haematologic reserve have not been studied in clinical trials"*.
At CHMP's request the MAH provided a review of haematology data (white blood cell count, absolute neutrophil, platelet and haemoglobin) from clinical trials (3800 imiquimod and 1170 vehicle patients) and postmarketing (56 spontaneous reports of haematologic events).

Consequently, the following information is added to the product information in line with CHMP's recommendation:
Section 4.8: *"Reductions in haematological parameters requiring clinical intervention have been reported from postmarketing experience."*
Section 4.4: *"Imiquimod should be used with caution in patients with reduced haematologic reserve.'*
Additionally reductions in haematological parameters requiring clinical intervention are included in the Risk Management Plan and CHMP requested that the MAH should commit to closely monitor reports alluding to immune thrombocytopenia and provide a review with the next Periodic Safety Update Report. In addition, the MAH should provide an interpretation of haematological side effect, in order to be able to identify patients at risk for these side effects.

In conclusion the most frequently reported adverse reactions to imiquimod are application site reactions, but systemic reactions, such as myalgia, arthralgia, fatigue, anorexia, depression and reductions in haematological parameters have also been reported. These systemic reactions may plausibly be explained by the action of cytokines induced by imiquimod.

EU Risk Management Plan (RMP)
The MAH has submitted a RMP upon CHMP request. The MAH has committed to revise the RMP in line with CHMP suggestions for improvement within 60 days of the CHMP's final opinion.

The MAH has committed to perform a comparative clinical trial with a three-year follow-up period within the timelines specified in the Risk Management Plan. The design of the trial should be subject to scientific advice (submission for CHMP scientific advice within 60 days of approval, final protocol within 12 weeks of obtaining scientific advice, initiation of trial by Q3/2007, final study report Q4/2011).

4 Overall discussion

Actinic keratoses are a common sun-induced precancerous lesions confined to the epidermis. Prevalence increases with advancing age. Lesions may regress spontaneously, with annual regression rates of approximately 25%. On the other hand, actinic keratoses may progress to squamous cell carcinoma with a potential to metastasize estimated at around 3-6%. The chance of any given lesion developing into a squamous cell carcinoma is unknown. Relative risks depend on factors related to the lesion itself (e.g. thickness) as well as individual patient characteristics. Patients with actinic keratoses at thermal injuries and large scars, with immunosuppression, human papilloma virus infection and lesions on mucosal surfaces have an increased risk of malignant transformation. The primary rationale of treating actinic keratosis is the prevention of progression to squamous cell carcinoma.

Treatment options for actinic keratosis include destructive modalities such as cryotherapy and electrodessication and curettage, and topical treatments such as 5-fluorouracil, diclofenac and methyl-5-aminolevulinate. Despite the fact that the primary rationale for treating actinic keratosis is the prevention of progression to squamous cell carcinoma, there are no robust clinical trial data available for any of the topical treatments licensed in Europe in this "prevention indication".

On the basis of the submitted data, it can be concluded that the short-term benefit of imiquimod in clearing of visible actinic keratosis lesions in immunocompetent patients has been established. As there are no data to establish non-inferiority to other treatments, preferential use of imiquimod over other topical therapies would be unjustified.

The demonstrated efficacy of imiquimod is limited to certain types of lesions (non-hyperkeratotic, non-hypertrophic) and locations (face and scalp) and appears to decrease with increasing numbers of lesions (1511-IMIQ). There are no data on efficacy in those patients with increased risk of malignant transformation as outlined above as patients with immunosuppression and those who had any dermatological disease or condition in the treatment or surrounding area that might have caused difficulty with examination were excluded from the clinical trials. Also, there are no data on actinic cheilitis.

The short-term efficacy of imiquimod in clearing actinic keratosis is within the range reported in literature for other topical treatments and more recent data for cryotherapy, but there are no data directly comparing the efficacy of imiquimod at the proposed posology with any established treatments for actinic keratosis, either short- or long-term.

Given that the benefit in the prevention of progression to squamous cell carcinoma has not been established and that several other treatment options are available, the ("absolute" and comparative) safety profile is of primary concern. Although the data made available at various steps throughout the procedure have allayed the concern that imiquimod is associated with an excess rate of recurrence and progression rates at one year, it is noted that only a subgroup of patients were followed up and no assessment was made as to whether SCCs arose from previous lesions. Therefore the MAH commits to conduct a long-term comparative trial as a post-approval commitment. This trial is to include assessments of recurrence and progression rates and time to recurrence as well as identified and potential risks.

Imiquimod may cause a variety of systemic reactions including stimulation or exacerbation of (auto)immune conditions, skin reactions resulting in hospitalisation and reductions in haematological parameters. Although the number of cumulative cases of such events is low in the context of the exposure and some of the reported cases may not be causally associated with imiquimod therapy, some demonstrate good temporal association with positive de-challenge and/or rechallenge.

Given that the proposed patient population is likely to be elderly and suffer from concomitant diseases (e.g. occult carcinoma with reduced haematologic reserve) that may make them more vulnerable to some of imiquimod's adverse effects, the condition to be treated in itself is not malignant, the established benefit is limited to clearing certain types of actinic keratosis lesions, and treatment options with a more favourable safety profile are available, CHMP considered that the indication should be restricted to *immunocompetent adult patients when size or number of lesions limit the*

efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate

5 Changes to the product information

Summary of Product Characteristics

The CHMP requested the following amendments to the proposed SPC:

Section 4.1 "Therapeutic indications"
"Imiquimod cream is indicated for the topical treatment of (…) clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs) on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate."

Section 4.2 "Posology and method of administration"
Posology
Actinic keratosis in adults
"Treatment should be initiated and monitored by a physician. (…) Sufficient cream should be applied to cover the treatment area. After a 4-week treatment-free period, clearance of AKs should be assessed. If any lesions persist, treatment should be repeated for another four weeks.
The maximum recommended dose is one sachet. The maximum recommended treatment duration is 8 weeks.
An interruption of dosing should be considered if intense local inflammatory reactions occur (see section 4.4) or if infection is observed at the treatment site. In this latter case, appropriate other measures should be taken. Each treatment period should not be extended beyond 4 weeks due to missed doses or rest periods.
If the treated lesion(s) show an incomplete response at the follow-up examination at 4-8 weeks after the second treatment period, a different therapy should be used (see section 4.4)."

Section 4.4 "Special warnings and special precautions for use"
Consequential changes have also been introduced in the sections 4.4 "Special warnings and precautions for use".

External genital warts, superficial basal cell carcinoma and actinic keratosis:
"Imiquimod should be used with caution in patients with reduced haematologic reserve (refer to section 4.8d)."
Actinic keratosis
"Lesions clinically atypical for AKs or suspicious for malignancy should be biopsied to determine appropriate treatment."
"There are very limited data available on the use of imiquimod for the treatment of actinic keratoses in anatomical locations other than the face and scalp. The available data on actinic keratosis on the forearms and hands do not support efficacy in this indication and therefore such use is not recommended."
"Imiquimod is not recommended for the treatment of AKs lesions with marked hyperkeratosis or hypertrophy as seen in cutaneous horns."
"No data are available on re-treating actinic keratoses that have cleared after one or two courses of treatment and subsequently recur, and any such use is therefore not recommended.
Data from an open-label clinical trial suggest that subjects with more than 8 AKs lesions showed a decreased rate of complete clearance compared to patients with less than 8 lesions."

Section 4.8 "Undesirable effects"
This section was updated to include the safety information derived from the clinical studies assessed. The revision takes into account the Adverse Events reported and their frequency.

c) Frequently occurring adverse events:
Actinic keratosis
"In clinical trials of imiquimod cream 3x weekly for 4 or 8 weeks the most frequently occurring application site reactions were itching at the target site (14%) and burning at the target site (5%). Severe erythema (24%) and severe scabbing and crusting (20%) were very common."

d) Adverse events applicable to all indications:
Clinical studies investigating the use of imiquimod for the treatment of actinic keratosis have detected a 0.4% (5/1214) frequency of alopecia at the treatment site or surrounding area. Postmarketing reports of suspected alopecia occurring during the treatment of sBCC and EGW have been received.

Reductions in haematological parameters requiring clinical intervention have been reported from postmarketing experience.

Rare cases of remote site dermatologic drug reactions, including erythema multiforme, have been reported from clinical trials. Serious skin reactions reported from postmarketing experience include erythema multiforme, Stevens Johnson syndrome and cutaneous lupus erythematosus.

Section 5.1 "Pharmacodynamic properties"
The revision of the Section 5.1 "Pharmacodynamic properties" of the SPC includes the description and the results of the studies assessed.

Actinic keratosis:
Clinical efficacy:
The efficacy of imiquimod applied 3 times per week for one or two courses of 4 weeks, separated by a 4 week treatment-free period, was studied in two double-blind vehicle controlled clinical trials. Patients had clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AKs lesions on the balding scalp or face within a contiguous 25 cm^2 treatment area. 4-8 AKs lesions were treated. The complete clearance rate (imiquimod minus placebo) for the combined trials was 46.1% (CI 39.0%, 53.1%).

One-year data from two combined observational studies indicate a recurrence rate of 27% (35/128 patients) in those patients who became clinically clear after one or two courses of treatment. The recurrence rate for individual lesions was 5.6% (41/737). Corresponding recurrence rates for vehicle were 47% (8/17 patients) and 7.5% (6/80 lesions). The rate of progression to squamous cell carcinoma (SCC) was reported in 1.6% (2/128 patients).

There are no data on recurrence and progression rates beyond 1 year.

The changes in the Section 5.2 "Pharmacokinetic properties" of the SPC reflect the addition of the new indication.

Package leaflet
Where relevant, above changes are also reflected in the package leaflet. Additionally the package leaflet has been amended following user testing results. The MAH also took the opportunity of this variation to amend the list of local representatives for Iceland, the Netherlands, and Estonia.

Furthermore, the PI was updated in line with the QRD 7 template. Additionally the MAH corrected a number of errors in translation that have been identified in all language versions except Czech.