

London, 14 July 2004  
Product name: **ALDARA**  
Procedure No. **EMEA/H/C/179/II/20**

## **SCIENTIFIC DISCUSSION**

## **1 Introduction**

The proposed amendments relate to an update of the SPC and consequential changes to the PL of Aldara 5 % cream, to extend the indication to include patients with superficial basal cell carcinoma.

The Marketing Authorisation Holder (MAH), 3M Pharmaceuticals (3M) 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. The MAH received CPMP Scientific Advice in September 2000 (CPMP/1882/00) for the intended variation.

The early development program studied both superficial basal cell carcinoma (sBCC) and nodular basal cell carcinoma (nBCC). The MAH has chosen to pursue the indication for sBCC.

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. Occurrence of tumour cells is accompanied by changes consistent with a triggering of cell-mediated immunity.

### **1.1 Proposed new indication**

Imiquimod cream is indicated for the topical treatment of external genital and perianal warts (condylomata acuminata) and superficial basal cell carcinoma in adult patients.

### **1.2 Proposed posology and method of administration**

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

#### ***Posology for sBCC***

Apply imiquimod cream for 6 weeks, 5 times per week (example: Monday to Friday) prior to normal sleeping hours, and leave on the skin for approximately 8 hours.

#### ***Method of administration for sBCC***

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, including one centimetre of skin surrounding the tumour. 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 recommended 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.

### **1.3 Problem statement**

Basal cell carcinoma (BCC) is a very common skin cancer, almost exclusively of white populations. Basal cell carcinoma is an unusual cancer in that it grows slowly and is locally invasive, but does not often metastasise. It is rarely fatal, but if not treated can result in extensive local tissue damage, and can track along embryonic fusion planes or nerve tracts producing morbidity and deformity. Tumours are often multiple, even when the patient is first seen. Along with other non-melanoma skin cancer (NMSCs), new BCCs are highly likely to appear over time, in particular within the first year after treatment of the primary lesion and treatment of patients developing large numbers of tumours presents a management problem.

Biopsy with histopathology confirms the diagnosis of clinically suspicious lesions. A number of histological subtypes have been described which differ in clinical presentation and risk of recurrence after initial treatment.

The majority of BCCs are low risk, the most common pattern being nodular, which accounts for 45%-60% of cases. Clinically these appear as translucent, light-coloured, pearly papules with telangiectasia, especially on the face, ears and neck. The superficial subtype is also low risk. It accounts for approximately 15%-35% of BCCs, is frequently multiple, and presents clinically as red, scaly macules or plaques, primarily on the trunk or the extremities. High risk BCCs include infiltrative, morpheaform (sclerosing), and micronodular subtypes, which tend to infiltrate more diffusely such that subsequent recurrence is more common. The nodular subtype, especially, may become pigmented. It can resemble a seborrheic keratosis, and occasionally malignant melanoma has to be considered in the differential diagnosis.

Cancer registries often summarise BCC together with squamous cell carcinoma (SCC) under the single label of NMSC, and rates for the individual histological subtypes are even more difficult to identify. Despite these limitations, BCC is considered the most common skin cancer in white adults. The annual incidence in Europe is estimated between 40 – 140 cases per 100 000, and has been rising markedly over the last 20 years, coming to represent a significant burden on health care systems. Incidence rates increase with age, and most patients present after age 60. Generally speaking BCC is more common in men than women, especially in the older age groups, although the sex ratio for sBCCs seems more equal.

### ***Pathogenesis of BCC***

BCCs are skin cancers which are thought to develop from stem cells of the basal layer of the epidermis as a result of DNA damage from intermittent exposure to sunlight. Continuing exposure to ultraviolet B radiation further impairs immune defences and over time immune surveillance breaks down so clinical disease becomes apparent.

### ***Currently available therapies for BCC***

Current approaches to treat BCC employ a variety of physical or chemical methods:

- Simple surgical excision consists of an excision with predetermined margin of surrounding skin
- Cryotherapy
- Curettage and Electro desiccation.
- Photodynamic Therapy (PDT)
- 5-fluorouracil (5-FU) as a cytotoxic agent, administered topically

Aldara may offer the advantage to avoid surgery in patients who refuse it or to provide a more practical treatment.

## **2 Non-clinical aspects**

### **2.1 Pharmacology**

Imiquimod works by stimulating antigen-presenting cells via TLR7. Toll-like receptors (TLRs) are highly conserved pattern-recognition receptors that function as regulators and controllers of the immune system. Imiquimod also induces the production of interferon-alpha (IFN- $\alpha$ ), interleukin-12 (IL-12), and tumour necrosis factor- $\alpha$ , with a resulting cytokine cascade that may induce and/or support a Th1 (T helper 1) immune response. Interferon induction is a critical function of imiquimod for the treatment of viruses and tumours in animal models.

Three new reports on non clinical pharmacology are included in the variation application. Two further define the mechanism of action of imiquimod in cytokine induction. The third report examines the activity of imiquimod applied topically in a mouse model of UV-induced actinic keratosis lesions.

In response to the request by the CPMP, the MAH provided a discussion of the pharmacologic effects of imiquimod in the intact skin of hairless rats and mice and condyloma acuminata.

Imiquimod was not tested in any preclinical models of Basal Cell Carcinoma because the lesions are difficult to establish in normal mice and require transgenic mice that over-express the Sonic Hedgehog gene.

The CHMP therefore concluded that preclinical data demonstrating the potential pharmacological effect of imiquimod in superficial basal cell carcinoma are not available.

## **2.2 Toxicology**

Aldara 5% cream (imiquimod) was evaluated in a photocarcinogenicity bioassay in albino hairless mice exposed to simulated solar ultraviolet radiation (UVR). Animals were administered vehicle formulation or imiquimod cream three times per week (100 µl of 0.03, 0.1 and 0.3 % of imiquimod) and were irradiated 5 days per week for 40 weeks. Mice were maintained without treatment for an additional 12 weeks to give a total duration of 52 weeks. All groups of mice administered any formulation were exposed to 600 Robertson-Berger Units (RBU) weekly of simulated solar radiation (including UVA, UVB and visible light). Furthermore, there were 2 control groups irradiated at low level of UVR (600 RBU/ weekly) and high level (1200 RBU/ weekly) respectively.

Treatment with the vehicle resulted in a decreased time to acquire one or more tumours when compared with the low UVR control group. The inclusion of imiquimod in the vehicle did not decrease the time to acquire one or more tumours compared with the vehicle group and on the contrary this time is slightly increased at the highest level of imiquimod.

The CHMP requested that the proposed addition to section 5.3 (“Preclinical Safety Data”) of the SPC relating to the results of the photocarcinogenicity should be amended to include a comment on relevance to man of the vehicle effect on tumours (considering the different dosing schedule), and that the currently proposed information on a reduction in tumour formation in imiquimod-treated mice should be deleted as it is not relevant to prescribers.

### ***UV exposure schedule and treatment schedule***

The CPMP requested a critical discussion of the 5 days per week UVR exposure schedule and the three days per week test/ control substance administration schedule, based on a consideration of the study objectives, the clinical exposure regime and the available scientific information. The MAH was asked to explain the reasons for UVR exposure with no accompanying test/ control substance administration on two days, and consider the possible impact on study sensitivity.

The MAH clarified that the photocarcinogenicity study was conducted in support of the actinic keratosis indication (application now withdrawn) as this patient population is prone/ predisposed to sun damage and may have greater exposure to the sun. In sBCC the relationship to cumulative sun damage is less apparent. Clinical trials on actinic keratosis used 2-3 days per week exposure, and hence 3 days per week was used for the photocarcinogenicity study. Three times a week topical exposure was shown to be tolerable in the 2-year carcinogenicity study, and has been determined to stimulate the immune system. More frequent dosing can lead to down regulation of the immune system leading to weight loss and predisposition to infection. Five days per week application, as proposed for the sBCC indication, was not considered tolerable for mice.

There will be greater absorption of imiquimod in the mouse than man, as mouse skin is thinner than human skin and there will be oral ingestion in mice because of grooming. This is supported by a report on a 2-week dermal toxicokinetic study which demonstrated systemic exposure.

The photocarcinogenicity study was preceded by a nine week topical dosage range finding study which examined doses up to 0.6% three times a week, with and without UV radiation. There were deaths at 0.6% with none at 0.3%, suggesting that 0.3% was a Maximum Tolerated Dose. Other changes generally seen at 0.6% (and sometimes at 0.3%) were increased body weight gains, absolute spleen weights and relative spleen weights.

Five day/ week UVR exposure was justified on the basis that this frequency gives a reasonable tumour response. Reducing exposure to three days would result in delayed tumour response, and could result in loss of sensitivity. Furthermore, any change would preclude the use of the testing centre's historical control data.

The CHMP concluded that if the photocarcinogenicity study is considered in relation to the proposed AK indication (now withdrawn), the dosage range finding study presented shows that the concentration used and the frequency of application (3 days/week) were appropriate. No data relevant to 5 days per week application (frequency for the proposed sBCC indication) are presented, therefore it has not been shown experimentally that this frequency was unfeasible. Nevertheless, the photocarcinogenicity study does not provide any suggestion that imiquimod has photocarcinogenic potential.

The use of five days a week UV exposure and 3 days per week imiquimod exposure is difficult to support on a purely scientific basis. Adequate UV exposure could have been achieved over 3 days by increasing the level of radiation. From a pragmatic viewpoint, however, the use of a well-established UV exposure regime has the important advantage that reference can be made to historical control data.

### ***Survival rate***

In the photocarcinogenicity bioassay, topical administration of imiquimod in the vehicle had no effect or slightly reduced the vehicle dependent enhancement in UVR induced skin tumour development. Survival rate is low, and even null in some groups (high UVR control group, 0.03% and 0.3% imiquimod).

The MAH commented that survival rate depends on morbidity/ death and tumour burden and provided a summary of the reasons for the death of mice in each dose group.

Criteria for sacrifice are made using criteria designed to minimise animal suffering, but to also ensure that there are adequate data for assessment. The low and high concentration imiquimod groups were sacrificed slightly prematurely, but there is no evidence that survival was significantly affected by UVR exposure, or vehicle or test article administration. The CHMP considered that sufficient data were collected to fully assess the photocarcinogenic potential of imiquimod.

### ***Photosensitivity***

The photocarcinogenicity bioassay was not designed to test the photosensitivity (phototoxicity and photoallergy). As the skin surface area treated can be exposed to solar ultraviolet radiation, the CHMP requested to add a statement in the section 4.4 ("Special warnings and special precautions for use") of the SPC, that the skin surface area treated should be protected against solar exposure and to reflect this wording also in the Package Leaflet (PL).

The MAH has conducted standard phototoxicity, photoallergy and photoirritation clinical studies in human subjects. The results of these studies show that imiquimod 5% cream has minimal phototoxicity, photosensitivity or photoirritancy potential. The standard of care would be to advise patients who have already developed at least one skin malignancy to adopt sun avoidance and sun protection behaviours.

### ***Phototoxicity and photoallergy***

Phototoxicity and photoallergy have not been tested as is required in the NfG on photosafety testing. As a consequence, a warning to “protect the skin surface area treated against solar exposure” could be included in the 4.4 section of the SPC. However, with imiquimod therapy for genital and perianal warts, it is recommended that the application site should not be occluded.

With respect to the external genital and perianal warts indication (EGW), the statement warning against the use of an occlusive dressing arose from the fact that the use of occlusive dressings was not permitted under the conditions specified in the clinical trials for that indication. In dermatology occlusion is used so that covering the skin causes moisture to be retained in the skin. The macerated skin is less efficient as a barrier and so active drug is able to penetrate to a greater extent. No comment was specifically made about exposure to sunlight, since the treated areas were - due to their anatomical location in the genital and perianal region - generally protected from exposure.

The statements not to use occlusive dressings in EGW and to protect the treated area from solar exposure in sBCC are, therefore, considered not to be contradictory.

The statements not to use occlusive dressings and to protect the treatment area from solar exposure have been added to the SPC.

### 3 Clinical aspects

#### 3.1 Clinical Pharmacology

The MAH has submitted a total of eight pharmacology studies: one of which assesses pharmacokinetics, five assess initial tolerability, and two assess pharmacodynamics in basal cell carcinoma. The studies are listed in table 1.

Table 1: List of clinical pharmacology studies

Study	Methodology	Dose frequency/ duration of treatment	Results
1402	Phase I open-label safety study in 58 subjects with AK lesions; imiquimod was applied to either face, scalp, or hands/arms	Imiquimod (250 mg) 3x/week for 16 weeks Face group: 1 sachet/dose Scalp group: 2 sachets/dose Hands/arms group: 6 sachets/dose	Systemic imiquimod serum concentrations were generally low, providing a large safety margin. Using the calculated area-under-the-curve values, safety margins for the 3 topical doses were found to be 303, 128, and 11, respectively
1244	Phase I, vehicle- controlled, photocontact allergenicity study evaluating imiquimod in 2 cohorts of 60 healthy subjects each; doses applied to lower midback.	Imiquimod and vehicle cream (200 µl)[a]: 2x/wk for 3 wks followed by a challenge dose (applied to 2 sites) 10-14 days post last dose	No detectable photocontact allergenicity potential. Photoirritation was reported by 42% (25/60) of subjects during the induction phase. No SAEs.
1249	Phase I, open-label, vehicle-controlled, 4-day safety study to assess the phototoxic potential of imiquimod in 21 healthy subjects; doses applied to lower midback.	Imiquimod and vehicle cream (200 µl): Single dose in duplicate / 24 hours	No detectable phototoxic potential was observed or reported for either imiquimod or vehicle. No AEs were observed or reported during the study.
1270	Phase I, open-label, vehicle-controlled, 21-day cumulative irritation study in 40 healthy subjects; doses applied to forearm (sun-damaged skin) and upper arm (normal skin).	Imiquimod and vehicle cream (200 µl): 7x/week (in duplicate) for 3 weeks	Imiquimod less irritating to sun-damaged skin than normal skin. At least 1 AE was reported by 82.5% (33/40) of subjects. There were no SAEs.
1281	Phase I, randomised, 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 3weeks, then 1x/d (Mon-Th) for 1 week	Sunburn cell and pyrimidine dimer analyses showed that imiquimod did not increase the response of white skin to UVR exposure. No LSRs were observed during the course of this study. There were no SAEs.
1359	Phase I, randomised, double-blind, vehicle-controlled study in 24 healthy volunteers; exploring histologic response in 'black' and 'white' (sic) healthy subjects. Doses applied to arm	Imiquimod and vehicle cream (250 mg): 3x/week for 4 weeks, or 7x/week for 4 weeks	Minimal histological changes noted in healthy skin. No trends were seen between imiquimod- and vehicle-treated sites or any dose frequency related trends between the imiquimod treatment groups.
1424	Phase I, open-label, mechanism of action study in subjects with histologically confirmed sBCC	Imiquimod 5x/week until signs of erosion or a max of 6 weeks	Findings suggest that imiquimod treatment may have a direct or indirect effect on tumour defence mechanisms and local immune activation. Erosion at the target tumour site occurred for all subjects within 3 weeks of dosing. There was 1 SAE.
1425	Phase I, open-label study in subjects with sBCC	Imiquimod, 5x/week: 8 subjects dosed until signs of erosion or a max of 6 weeks, 6 subjects dosed for either 1, 2, or 4 weeks; Vehicle 5x/wk for 2 weeks (4 subjects)	Cell infiltrates consistent with imiquimod mediating tumour destruction by an immune-mediated mechanism. Application site reactions only reported in the imiquimod group. There were no SAEs.

##### 3.1.1 Pharmacodynamics

The objective of study 1424 was to determine if imiquimod or a cytokine would diminish the ability of the superficial basal cell carcinoma (sBCC) tumour to avoid immune destruction by evaluating baseline and mid-regression biopsies. Subject eligibility was determined at the prestudy visit and upon receipt of dermatopathologist confirmation of an sBCC tumour. Subjects returned to the study centre weekly until the target tumour began to show signs of erosion; at this point, the tumour was surgically excised, sectioned, and stored in formalin, or was fresh frozen. If erosion did not occur at the target tumour site, the tumour was surgically excised after 6 weeks of treatment.

Pre- and post-treatment biopsy specimens from 6 subjects were evaluated for B-cell lymphoma-2 protein (Bcl-2), intercellular adhesion molecule (ICAM)-1, Fas-ligand (Fas-L), IL-10, IFN- $\gamma$ , cluster designation (CD) 4, CD8, and transporter associated with antigen processing (TAP)-1. Routine haematoxylin and eosin staining was used to determine the percentage and density of infiltrating cells from circulating blood. Of the biomarkers evaluated, only B-cell lymphoma-2 protein Bcl-2 showed an 'improvement' (decrease) in the majority of patients (4/6). The data are considered insufficient to support the addition of the proposed statement (section 5.1 of SPC) that imiquimod reduces the defence mechanisms of superficial basal cell carcinoma.

Study 1425 was a non-randomised open-label, vehicle-controlled, pilot study to evaluate the cellular infiltration into a basal cell carcinoma (clinically diagnosed) after treatment with imiquimod 5% cream 5x/week for 1, 2 or 4 weeks.

Immunohistochemistry results demonstrated infiltration with CD4+ T-cells, dendritic cells, macrophages and CD8+ T-cells, and comparatively few neutrophils or  $\gamma/\delta$  T-cells, suggesting that imiquimod has an immune-mediating tumour destruction mechanism that is similar to classic cell-mediated immune reactions in skin. The data are insufficient to support the statement that imiquimod stimulates the infiltration of tumour-destructive cells in superficial basal cell carcinoma. A number of subjects did not have a diagnosis of BCC. No direct comparison can be made to the effects of vehicle at reference time points.

### **3.1.2 Tolerability studies**

#### ***Histological effects in white vs. black skin***

Study 1359 explored the differential histological effect in white vs. black skin, and the effects on melanocytes in 24 healthy subjects. Imiquimod and vehicle cream was applied daily or 3x/week dosing for 28 days or until development of an intense erythematous reaction. Approximately 52.6% of all biopsies showed no pathological change (*histologically normal skin*). Another 31.5% showed only mild superficial perivascular dermatitis. No significant histological changes were observed and only small and inconsistent changes in melanocytes and melanophages numbers which showed no clear relationship to drug exposure.

#### ***Skin irritation study on sun-damaged versus normal skin***

Study 1270 was an open-label, vehicle-controlled 21-day study to assess the skin irritation potential of imiquimod 5% cream and vehicle cream to sun-damaged and normal skin areas. 40 healthy volunteers applied approximately 0.2 ml imiquimod 5% cream (10.0 mg imiquimod) and vehicle daily for 21 days. The sun-damaged skin had a lower incidence and severity of irritation (8% of the subjects had minimal erythema) compared to the normal skin (15% of the subjects had minimal erythema, 10% of the subjects had definite erythema and 3% intense erythema).

#### ***Photocontact Allergenicity***

Study 1244 was an open-label, vehicle-controlled, 6-week photocontact allergenicity study in healthy Caucasian subjects of skin type classification I-III. No subjects had a photocontact allergenicity reaction to either imiquimod 5% or vehicle cream. However, in the first cohort of 60 subjects, 42% of the imiquimod and 38% of the vehicle treated sites had maximum skin irritation scores of  $\geq 3$  (intense erythema) during the study. Alternation of patch application sites for the second cohort of subjects resulted in less skin irritation.

#### ***Photoirritation***

Study 1281 was conducted to investigate the effect of imiquimod on sunburn cell induction and pyrimidine dimer formation in 41 healthy subjects of skin types I - III. Overall, this study showed that imiquimod did not increase the response of white skin to UV exposure.

#### ***Phototoxicity***

Study 1249, an open-label, vehicle-controlled, 4-day study to assess the phototoxic potential of imiquimod 5% cream in 21 subjects with skin types I-III, revealed no detectable phototoxic potential for imiquimod 5% cream or vehicle.

### 3.1.3 Pharmacokinetics

The pharmacokinetics of imiquimod cream, 12.5mg – 75mg, 3x/week for 16 weeks, were studied in 58 subjects with actinic keratosis. Imiquimod serum concentrations after topical administration were generally low. A 2- to 4-fold accumulation of imiquimod in serum was observed with multiple dosing. Urinary recovery of imiquimod and metabolites combined accounted for  $\leq 0.52\%$  of the dose. Safety margins comparing pharmacokinetic parameters following topical application to those following oral doses of 100 mg and 300 mg that produced no IFN induction ranged from 36 (hands/arms) to 1940 (face) for  $C_{max}$  and from 11 (hands/arms) to 597 (face) for AUC.

The mean imiquimod  $C_{max}$  and AUC following administration of oral and topical doses of imiquimod are given in table 2.

Table 2: Mean imiquimod  $C_{max}$  and AUC following administration of oral and topical doses of imiquimod

Dose (mg)	AUC <sub>0n</sub> (ng.hr/ml)	C <sub>max</sub> (ng/ml)
<b>Topical</b>		
12.5	2.06	0.120
25	4.89	0.214
75	55.4	3.53
<b>Oral</b>		
100	625	126
200	1229	232
200	2222	320
300	4877	493

The MAH states that in study 1402, the levels of biomarkers sensitive to imiquimod cream (interleukin-1 antagonist, interferon- $\alpha$ , and 2'5'-oligoadenylate synthetase) increased nearly 10-fold over baseline, and states that the production of these biomarkers was not associated with any systemic adverse event.

The MAH was requested to discuss these findings in more detail, in particular with a view to systemic interferon levels and adverse events observed in the study that might be plausibly explained by interferon. Also, the relevance of the increases of interleukin-1 antagonist and 2'5'-oligoadenylate synthetase should be discussed. Information regarding systemic interferon levels should be added to section 5.1 of SPC (“Pharmacodynamic Properties”).

The MAH has provided a satisfactory response to this request, including an overview of flu-like symptoms in relation to data on biomarkers.

Data obtained in the pivotal studies show that the incidences of flu-like symptoms, fatigue, fever, and myalgia were numerically slightly higher in subjects treated with imiquimod 5x/week. The difference was not statistically significant. Headache (7.6 vs. 2.2%) was reported significantly more often in imiquimod treated subjects.

It is biologically plausible that some of the adverse effects of topical imiquimod are caused by systemic induction of cytokines, e.g. the observed reduction in haematological parameters. The data clearly show that the systemic levels of alpha interferon and other cytokines increased following repeat administration of topical imiquimod. It was therefore considered that physicians should be informed this fact. The MAH revised the SPC proposal accordingly.

## 3.2 Clinical Efficacy

The clinical programme for sBCC includes 19 trials. Of these, only 3 phase III and two phase II trials assess the intended patient population, dosing interval and duration of treatment. Table 3 gives an overview of these studies.

Table 3: Overview of relevant trials - sBCC

Study Number	Design	Total no. of patients	Treatments	Target lesion(s)	Histological response rates % (dosing group)
<b>Phase III</b>					
1393	Randomised double-blind, parallel-group, vehicle-controlled	362	Imiquimod 5x/week (n=94) Imiquimod 7x/week (n=89) Vehicle 5x/week (n=89) Vehicle 7x/week (n=90)	Primary, non-infected, not previously treated, single sBCC ≤2cm	78 (5x) 88(7x)
1408	Randomised double-blind, parallel-group, vehicle-controlled	362	Imiquimod 5x/week (n=91) Imiquimod 7x/week (n=90) Vehicle 5x/week (n=90) Vehicle 7x/week (n=91)	As above	87 (5x) 71 (7x)
1412	Long-term (5-years) open-label, uncontrolled	182	Imiquimod 5x/week	Single sBCC ≤2cm	No histological results available. Initial clinical response rate: 90% (5x)
<b>Phase II</b>					
1431	Randomised, open-label, parallel-group (5x/week and 7x/week), uncontrolled	67	Imiquimod 5x/week (n=36) Imiquimod 7x/week (n=31)	2-6 sBCCs ≤2cm primary, non-infected, not previously treated	Histological response rate for all target tumours: 77% (both 5x and 7x).  Histological response rate per patient: 47 (5x), 58 (7x)
1432	Open-label, uncontrolled	66	Imiquimod 5x/week	Single large (≥ 2cm) BCCs	86% (5x)

### ***Dose response studies***

Dosing frequency in the 19 efficacy/ safety trials ranged from a single application once a week to twice daily applications seven days a week, and duration of treatment from six to sixteen weeks. All trials test imiquimod 5% cream, no other strengths were investigated.

The highest frequency (twice daily seven times per week) was discounted on tolerability grounds. Study 1305, a randomised, double-blind, vehicle-controlled phase II study demonstrated histological response rates of only 52% for the 3x/ week as compared to 81% for the 5x/ week dosing group; on the basis of these results the 3x/ week dosing schedule was excluded from further development.

Assessment of the optimum dosing frequency was performed by pooling the data from studies 1393 and 1408 and comparing the safety and efficacy results of imiquimod five times weekly or daily across trials: At 5x/ week or 7x/ week efficacy was comparable with histological response rates of 82% for the five times weekly and 79% for the daily dosing groups. Based on the better local adverse effects profile, the 5x/ week dosing schedule was chosen.

Imiquimod 5% cream is clearly more effective than vehicle in the treatment of sBCC. However, the following remarks can be made:

#### *Strength of imiquimod cream*

All trials tested the 5% strength. It is not clear if a similar effect could have been achieved with a 1% formulation. The 5% formulation was shown to be significantly more effective than the 1% formulation in two external genital warts trials. These results may be extrapolated to sBCC. This issue is therefore not considered to be of major concern.

#### *Duration of treatment*

The applicant states that the treatment duration chosen for the phase III studies was 6 weeks because in the Phase II studies, daily dosing for 12 weeks (study 1305) did not show an increase in efficacy over 6 weeks (study 1291). However, it is possible that a shorter treatment duration may be sufficient. Results from the only study evaluating treatment periods less than 6 weeks (study 1418), albeit in a small number of patients with either sBCC or nBCC, indicated identical complete histological response rates for four and six weeks treatment duration (67%, 8/12 each).

#### *Dosing frequency*

No dose response studies were performed to directly compare five times weekly with three times weekly treatment at the recommended treatment duration for six weeks, but this is not considered an issue as the relationship between dose frequency and response was consistent across the development programme, with increasing dose frequency (up to 5x/week) leading to higher response rates.

### **Main studies**

#### *Methods*

Two phase III trials of identical design evaluated the posology proposed for licensing. One-year safety data and one-year recurrence rates are available from a further ongoing trial.

Trial 1393 was a randomised, vehicle-controlled, double-blind, parallel group study to assess the efficacy and safety of imiquimod 5% cream for the treatment of superficial basal cell carcinoma, performed at 31 US sites between January 2001 and August 2002.

Trial 1408, of identical design, was performed at 28 sites in the US between February 2001 and September 2002.

Trial 1412 is an open-label study to evaluate the safety and long-term clinical efficacy of imiquimod 5% cream applied once daily 5 days per week in the treatment of sBCC. The trial is ongoing at 27 European sites. It started in February 2001, with the treatment period being completed in November 2001. The long-term follow-up phase is ongoing.

Subjects were required to have one primary, not recurrent, not previously treated, non-infected superficial basal cell carcinoma without histological signs of aggressive growth patterns, located on the limbs, trunk, neck or head, with a minimum tumour area of 0.5cm<sup>2</sup> and a maximum diameter of 2.0 cm. Tumours on the head within 1 cm of the hairline, eyes, nose, mouth, or ears and those in the anogenital area were excluded. Hence, it is proposed that the indication be amended to better reflect the patient population studied in the pivotal trials.

All patients had histologically verified sBCC. This diagnosis was made by two independent blinded dermatopathologists. This may be taken as a reassurance regarding patient selection.

Less than 1% of patients (6 of 724) were referred after having been biopsied by another clinician. This is considered acceptable.

In studies 1393 and 1408, patients were randomised to treat the target tumour for six weeks with either imiquimod 5% cream or vehicle cream, either once daily for five consecutive days per week or daily, i.e. 7x/week. In study 1412, all patients treated the target tumour for six weeks with imiquimod 5% cream once daily for five consecutive days per week.

The objectives of studies 1393 and 1408 were to evaluate the efficacy (primary) and safety (secondary) of imiquimod 5% cream at each of 2 dosing regimens compared to vehicle in the treatment of one (1) sBCC tumour in subjects when the cream was applied for 6 weeks.

The primary objective of the ongoing trial 1412 was to assess the long-term sustained clearance rate, defined as the proportion of subjects who were clinically clear of sBCC at the 12-week post-treatment visit and remain clear during the 5 year follow-up period. Secondary objectives are the evaluation of the safety and cosmetic outcome.

The primary outcome measure in trials 1393 and 1408 was the complete response rate. This was a composite endpoint, defined as the proportion of patients who at the 12-week post-treatment visit:

1. had neither clinical (visual) nor histological evidence of sBCC at the target tumour site; or
2. who had clinical (visual), but not histological evidence of sBCC at the target tumour site, with histological findings providing an explanation of the clinical assessment.

This endpoint is considered rigorous.

### Results

362 patients each were included in trials 1393 and 1408; 182 patients were included in trial 1412. All randomised subjects were included in the ITT analyses. Target tumours were mainly located on the trunk and on the extremities. Tumours on the neck and face accounted only for a small minority of tumours in all pivotal studies. The response rates are given in table 4.

Table 4: Response rates

<i>Complete response rates in % (ITT)</i>				
Study	Imiquimod 5x/week	Vehicle 5x/week	Imiquimod 7x/week	Vehicle 7x/week
<b>1393</b>	70	2	80	0
<b>1408</b>	80	1	66	3
<i>Histological response rates in % (ITT)</i>				
Study	Imiquimod 5x/week	Vehicle 5x/week	Imiquimod 7x/week	Vehicle 7x/week
<b>1393</b>	78	6	88	1
<b>1408</b>	87	1	71	4

A positive correlation was seen between response rates and intensity/severity of local skin reactions (erythema, erosion, scabbing/crusting). As local skin reactions became more severe, a higher proportion of subjects were complete responders.

The results of a pooled analysis of studies 1393 and 1408 are given in table 5.

Table 5: Pooled analysis of studies 1393 and 1408

<i>Pooled analysis of pivotal phase III studies 1393 and 1408: Response rates in % (95%CI) ITT</i>				
	Imiquimod 5x/week	Vehicle 5x/week	Imiquimod 7x/week	Vehicle 7x/week
Composite response	75 (68, 81)	2 (1, 5)	73 (66, 79)	2 (1, 5)
Histological response	82 (76, 87)	3 (2, 7)	79 (73, 85)	3 (1, 6)

No statistically significant subgroup effects were found for sex, age, race, sex and age, and geographic area.

In study 1412, the clearance rate at 12 weeks post-treatment (assessed clinically, but not histologically) was 90%, and the estimated sustained clearance rate at 12 months was 92.7% (87.9-97.4). 163/182 patients were clinically clear of sBCC at 12 weeks post-treatment; 10 of who had a recurrence within 12 months. Data provided at one year (study 1412) are not considered sufficient to assess sustained efficacy and/or recurrence. It is noted that no data was provided at one year (1412) on overall cosmetic assessment.

### **Supportive Studies**

#### *Multiple sBCCs*

Study 1431, an open-label, parallel-group study assessed efficacy and safety of imiquimod 5% cream, 5x/ week or 7x/ week for six weeks, in 67 subjects with 2-6 multiple superficial basal cell carcinoma lesions.

Efficacy outcomes are summarised in table 6.

Table 6: Response rates study 1431

<i>Multiple sBCCs - Response rates per patient – ITT analysis</i>		
	Imiquimod 5x/week	Imiquimod 7x/week
Complete response <sup>1</sup>	44	55
Histological response <sup>2</sup>	47	58
Partial response rates <sup>3</sup>	89	84

<sup>1</sup> proportion of subjects with no clinical evidence of sBCC

<sup>2</sup> proportion of subjects with no histological evidence of sBCC in all their target tumours

<sup>3</sup> proportion of subjects with 50% or more of their of sBCC showing clearance

The histological response rate determined on a *per tumour* level was 77% in all dosing groups. A positive association was demonstrated between tumour histological response rate and severity of erosion, erythema and scabbing/crusting.

As the above results stemmed from an open label uncontrolled study in a small number of patients, the CHMP concluded that this data was not robust enough to warrant inclusion into the SPC.

#### *Large ( $\geq 2$ cm) sBCCs*

Study 1432, an open-label, uncontrolled phase II study, looked specifically at the clinical problem of large tumours. A total of 66 subjects with sBCCs on the trunk or arms that exceeded 2 cm in at least 1 dimension were treated with imiquimod 5x/ week for 6 weeks. At the 12-week post treatment visit, only subjects with tumours judged clinically suspicious had a full surgical excision. For subjects judged clinically clear, histology was limited to biopsies, as it was not considered ethical to excise a large area of clinically normal skin. Thus the endpoint is not absolutely comparable to that in the 3 phase III, vehicle-controlled studies, but within this limitations, the complete response rate (ITT) of 83% seemed similar to that in the other studies. Efficacy outcomes are summarised in table 7.

Table 7: Response rates study 1432

<i>Large sBCCs - Response rates – ITT analysis</i>	
	Imiquimod 5x/week
Complete response	83%
Histological response	86%

The predicted probability of complete response by target tumour area indicated a negative relationship between tumour size and probability of complete response. When the target tumour area was categorised into quartiles, the downward trend was observed for tumour areas greater than 7.25cm<sup>2</sup>.

## **Discussion**

### *Therapeutic Indication*

The CHMP had requested that the indication of Aldara be amended to “*small superficial basal cell carcinomas*”, in line with the patient population studied in the clinical trials.

The CHMP discussed whether the indication should be restricted to “*Small superficial basal cell carcinomas not amenable to surgical excision*”, due to the lack of data on long term clearance rates beyond 12 months post-treatment and the fact that no comparative data versus surgery are available.

The CHMP concluded however, that such indication would not be in line with the design of the clinical studies, in which all tumours treated had to be amenable to surgical excision to allow for post-treatment excision to confirm clearance of the tumour. Furthermore, imiquimod local treatment is intended as alternative to surgery and other non-surgical options when treating sBCC.

### *Targeted BCC population*

The targeted BCC population was defined by the Applicant as patients with a minimum tumour area of 0.5cm<sup>2</sup> and maximum diameter of 2.0 cm. Patients with tumours in high risk areas (such as scalp, nose, mouth, ears, and eyes) were excluded from all studies except 1339-IMIQ. The CHMP requested that this should be reflected in the SPC, section 5.1.

### *Long term data*

The CHMP discussed whether the SPC should state that excision biopsy still has to be regarded as first-line therapeutic modality, as long-term data for treatment with imiquimod are not yet available.

Consequently the MAH proposed to include the following statement in section 4.4 of the SPC:  
“*As data on long-term clearance rates beyond 12 months post-treatment are not currently available, other appropriate therapeutic modalities should be considered for sBCC. Use of imiquimod cream may be considered as an alternative in cases where surgery is not desirable or a cosmetic outcome is regarded as important.*”

The CHMP concluded that the statement on cosmetic outcome was not supported by robust data. Furthermore, in line with the discussion above, the statement restricting the use of imiquimod to cases where surgery is not desirable, should be deleted.

The SPC was amended accordingly.

Data provided at one year are not sufficient to assess sustained efficacy and/or recurrence. The CHMP therefore requested the MAH to add information to section 5.1 of the SPC stating that no long-term data are available.

### 3.3 Clinical Safety

#### *Safety margins for systemic exposure*

Safety margins for systemic exposure to imiquimod following topical administration of imiquimod 5% cream were calculated in patients with actinic keratosis (study 1402) by comparing the mean  $C_{max}$  and mean AUC of imiquimod following topical administration with values observed following single oral doses of imiquimod 100, 200 and 300 mg (safety margin = mean  $C_{max\ po}$  / mean  $C_{max\ topical}$ ).

The safety margins for topical imiquimod, compared with single oral doses in humans known to induce systemic levels of IFN with clinically meaningful symptoms, were calculated as 36 to 1940 for peak exposure ( $C_{max}$ ) and 11 to 597 for total exposure ( $AUC_{0n}$ ).

Serum IFN was quantifiable in 50% – 67% of subjects following repeat topical dosing. The maximum individual IFN concentration was 564U/ ml. Median IFN concentrations following multiple dosing were higher ( $\leq 3$  fold) than those after single dose administration. Interferon is known to cause adverse reactions such as flu-like symptoms, depression, haematological disorders etc. Such adverse reactions/ events have been observed with imiquimod. Therefore, the CHMP requested that information on systemic levels of interferon be added to the SPC.

#### *Patient exposure and disposition in clinical trials*

The supplementary safety database for sBCC comprises a total of 1881 subjects exposed to imiquimod, 1574 with basal cell carcinoma (some data from the treatment of nodular rather than superficial BCC); 58 with actinic keratosis; and 249 healthy volunteers. In addition, 549 subjects received vehicle control. A further 59 subjects have been exposed in 3 ongoing studies and add to the at-risk population. The maximum cumulative dose for any individual treated for a sBCC was 306 mg. The maximum duration was 16 weeks and the most frequent dosing regimen studied was 2x/ day 7x/ week.

#### *Adverse events*

Seven (7) deaths occurred during the BCC clinical trial programme. None of the deaths were considered related to treatment.

Seventy-five (75) imiquimod-treated patients experienced 86 non-fatal serious adverse events in the sBCC studies. Of those, only one (non-Hodgkin lymphoma, persistent) was considered possibly related to imiquimod. No conclusion can be made from this single case.

Common and non-serious adverse events (NSAEs) data with incidences  $\geq 5\%$  were recorded for application site disorders (28.5%), body as a whole – general disorders (6.0%), central and peripheral nervous system disorders (6.2%), and respiratory system disorders (5.7%). When reviewed at the level of the preferred term, only application site reactions still exceeded a 5% threshold, and accounted for all the events that mapped to the corresponding body system.

The largest contributor to the reports appearing in central and peripheral nervous system disorders was headache, accounting for 8% of the total of 11%. Headache has been reported in association with systemic IFN treatment, and therefore, with an incidence  $>5\%$  and statistically different to vehicle, it seems plausible as a true treatment-related AE. Lymphadenopathy was seen to account for almost all the reports that mapped to white cell and resistance disorders.

Application site reactions such as erythema, oedema, induration, vesicles, erosion, ulceration, scabbing/ crusting and flaking/ scaling were observed frequently. The intensity of application site reactions appeared to be correlated to response rates. The majority of application site reactions resolved upon cessation of treatment.

The MAH states that confirmed skin infections suggest no association with imiquimod overall, yet treatment site infections confirmed by culture appear to occur at a higher incidence in imiquimod-treated patients than in vehicle-treated patients. Treatment site infections were reported as an adverse event in 36 patients with sBCC, 29 of which were confirmed by culture. Treatment in most cases consisted of a rest period only. In some cases topical and/ or systemic antibiotics were prescribed. There were no clinically significant sequelae. The CHMP requested that relevant information be added to section 4.8 of the SPC.

All treatment groups showed an increase in the scores for scarring. A significant increase of hypopigmentation was also observed. Rough/ dry/ scaly skin surface decreased in all groups after treatment. The CHMP requested that the SPC and the PL include information on hypopigmentation.

No specific statement was added regarding scarring since all patients involved in the pivotal trials had the tumour site biopsied for diagnosis prior to treatment and excised for histological examination post-treatment to confirm clearance of the tumour. Therefore it is not possible to differentiate the extent of any post-treatment scarring which is attributable to imiquimod therapy from that caused by the biopsy and excision.

### ***Laboratory findings***

Statistically significant decreases from baseline to end of treatment were found for haemoglobin, white cell count, and platelet count. The decreases were small and the mean levels generally remained within the normal ranges. In addition, individual case reports of significant reduction in haematological parameters were reported in the PSUR, covering the period 27 February 2002 to 26 February 2003.

In view of these adverse haematological findings, the CPMP requested a detailed expert safety review of the haematological changes reported from all clinical trials (independent of indication) and the marketed use of imiquimod. Also, the MAH should include information on the observed changes in haematology parameters in the SPC.

The MAH has submitted a satisfactory response to this point. The data confirm that topical imiquimod treatment results in modest decreases in haematologic parameters that are probably not of clinical concern. No conclusion about the impact of these changes can be made for patients with clinically significant haematologic conditions because such patients were excluded from the actinic keratosis and basal cell carcinoma trials.

However, the CHMP considered that physicians should be informed about the potential modest adverse effects of imiquimod on haematologic indices.

#### 4 Overall Discussion

The submitted data are considered to support the efficacy of imiquimod 5% cream in the topical treatment of small superficial basal cell carcinomas.

The recommended dosage schedule of 5x/ week is justified by data indicating that topical treatment 3x/ week results in a lower rate of histological clearance (52%) than 5x/ week (81%), whilst the clearance rates of 5x/ week was similar to that of 7x/ week.

The lower frequency of local adverse effects was clearly in favour of the 5x/ week dosing schedule.

It is not possible to determine from the submitted clinical data whether a six-week treatment schedule results in better response rates compared to for example four weeks. This is not considered a major public health issue that would preclude granting the variation.

No data are available to assess recurrence rates for up to 5-years following imiquimod therapy. Interim results from a long-term open-label uncontrolled study indicate an estimated sustained clearance of 92%, with 10 of 163 patients having clinical evidence of a recurrence within 12 months. The CHMP agreed that a condition for the approval of this variation should be that the applicant submits data on sBCC recurrences at yearly intervals and after the end of the ongoing long-term studies.

Limited data, derived from open-label uncontrolled studies in a small number of patients, are available for large sBCCs and for multiple sBCCs. These data appear to support the findings of the pivotal studies, with similar response rates on an individual tumour level when multiple tumours were treated, but lower response rates for larger tumours ( $>7.25\text{cm}^2$ ).

Local application of imiquimod 5% cream is associated with a significant number of adverse events, mainly consisting of local skin reactions that may be severe in a considerable number of patients. These skin reactions are considered to be related to the pharmacological effects and if required can be successfully managed by rest periods without compromising efficacy.

Adverse events probably caused by systemic interferon-levels, such as fatigue, fever, myalgia, were observed slightly more commonly in imiquimod-treated patients than in vehicle treated patients. The difference was not statistically significant.

Topical imiquimod treatment resulted in modest decreases in haematological parameters that are probably of no clinical concern. No conclusion about the impact of these changes can be made for patients with clinically significant haematological conditions because such patients were excluded from the trials. A relationship with drug exposure is considered biologically plausible.

No data are available to assess relative risk/benefit of imiquimod as compared to other non-surgical or surgical options. However, on the basis of the data presented, imiquimod may be considered a useful therapeutic option in the treatment of small superficial basal cell carcinomas.

In conclusion, the risk/benefit ratio for imiquimod in the proposed indication sBBC is considered positive.

## 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”

The indication should be reworded as follows: “*small superficial basal cell carcinomas*”

#### Section 4.2 “Posology and method of administration”

The CHMP requested that this section include the information that lesion response should be assessed after three months. Also, information should be given that lesion sites showing an incomplete response should be treated using a different treatment modality, with a cross-reference to section 4.4. (“Special warnings and special precautions for use”).

A recommendation should be given to temporarily interrupt treatment when treatment site infections are observed or when required by patient’s discomfort or severity of local skin reactions, with a cross-reference to section 4.4.

The recommendation “*After this period it is recommended that imiquimod cream is removed with mild soap and water*” should be amended to read “*After this period it is ~~recommended~~ **essential** that imiquimod cream is removed with mild soap and water*”.

#### Section 4.4 “Special warnings and special precautions for use”

The CHMP requested the following amendments:

##### *Information applicable to all indications*

Information applicable to all indications should be stated at the beginning of this section. This should also include a statement that the treatment site should not be occluded with tapes or bandages. This is already mentioned in the SPC for external genital warts and was also a precaution in the phase III studies for BCCs.

##### *Information applicable to BCCs*

The CHMP requested the addition of a precautionary statement reflecting the fact that until long-term data become available other appropriate therapeutic modalities should be considered for sBCC.

##### *Use of imiquimod for recurrent sBCCs*

The SPC should state that no clinical experience exists with the use of Aldara for recurrent and previously treated tumours. Therefore the use should not be recommended for tumours previously treated. Also, re-treatment with Aldara should not be recommended.

##### *Use of imiquimod for large sBCCs*

The SPC should include the information that data from an open-label clinical trial suggest that larger tumours (>7.25cm<sup>2</sup>) are less likely to respond to imiquimod therapy.

##### *Use of imiquimod for sBCC in immunocompromised patients*

The SPC should state that no clinical experience exists with the use of Aldara for sBCC in immunocompromised patients.

As the skin surface area treated can be exposed to solar ultraviolet radiation, the CHMP requested that a statement was added that the skin surface area treated should be protected from solar exposure.

#### Section 4.8 “Undesirable effects”

Since external genital and perianal warts, AK, and superficial BCC are different skin conditions and occur in different anatomical areas, side effect profiles were not combined and presented separately in the SPC. The CHMP requested that the information given in this section should be updated as requested at renewal to include MedDRA terminology. Adverse events considered at least possibly causally related to treatment, and with an incidence of  $\geq 0.1\%$ , should be included. The frequencies of adverse effects should be defined as outlined in the Guideline on Summary of Product Characteristics.

The CHMP requested that relevant safety information from the submitted new clinical studies is added. Information on treatment site infections should be added. The observed haematological effects should be listed.

The frequency of influenza-like illness was corrected to read 'uncommon'. Local adverse effects were described in more detail. Information regarding hypopigmentation was added.

### Section 5.1 "Pharmacodynamic properties"

The CHMP requested to add information regarding systemic alpha interferon and other cytokines following topical application of imiquimod.

The CHMP found that the data are insufficient to support the statement that imiquimod stimulates the infiltration of tumour-destructive cells in superficial basal cell carcinoma. A number of subjects did not have a diagnosis of BCC. No direct comparison can be made to the effects of vehicle at reference time points.

The CHMP concluded that the pharmacological program to investigate the mechanism of action included a low number of patients. There was no consistent evidence (statistical) that shows local immune-mediated response correlates with clearance. The data are considered insufficient to support the addition of the proposed statement that imiquimod reduces the defence mechanisms of superficial basal cell carcinoma. Consequently the CHMP requested that the corresponding proposed paragraph should be deleted.

The CHMP requested the MAH to include information on BCC population targeted in the majority of clinical trials (single primary superficial basal cell carcinomas with a minimum size of 0.5 cm<sup>2</sup> and a maximum diameter of 2 cm) and to inform that tumours located within 1 cm of the eyes, nose, mouth, ears or hairline were excluded from the studies.

Data provided at one year are not sufficient to assess sustained efficacy and/or recurrence. Therefore, the CHMP requested the MAH to add information stating that no long-term data are available.

### Section 5.2 "Pharmacokinetic properties"

The new method used detects systemic concentrations below 5 ng/ml. It is stated in the proposed SPC that "*The data defining systemic absorption of imiquimod are limited by the use of bioanalytical method with a 5 ng/ml lower limit of quantitation*". The CHMP requested that this sentence should be deleted. In addition, the following paragraph "*Percutaneous absorption of imiquimod cream has been studied over a wide spectrum of skin types, including healthy intact skin and the lesions of sun damaged skin. These studies should also encompass the likely pharmacokinetics of imiquimod cream across the affected skin of patients with superficial basal cell carcinoma/actinic keratosis. The percutaneous penetration of imiquimod cream following topical administration for 8 – 12 hours was minimal in all cases.*" should be deleted as this section concerns Actinic Keratosis patients and not a wide spectrum of skin types.

### Section 5.3 "Preclinical safety data"

The CHMP requested that the proposed addition relating to the results of the photocarcinogenicity should be amended to include a comment on relevance to man of the vehicle effect on tumours, and that the currently proposed information on a reduction in tumour formation in imiquimod-treated mice should be deleted as it is not relevant to prescribers.

### **Package Leaflet**

Where relevant, above changes are also reflected in the Package Leaflet (PL).

The PL is split into separate documents, one for each indication. This may possibly confuse patients. Also, it results in a lot of information being duplicated and some important information missing from the sBCC part of the PL, in particular, with regard to “Undesirable effects”.

Therefore, the PL text has been reformatted to present the information for each indication under a single heading, rather than separating out the indications completely. In the revised format, however, it has still proved necessary to indicate that certain information is specific to a particular indication.

In addition, the CHMP requested that BCC should be more clearly explained to patients. The CHMP also requested that the dosing instructions should be improved.

### **III. CONCLUSION**

The CHMP considered this Type II variation to be acceptable and agreed on the proposed wording to be introduced into the Summary of Product Characteristics and Package Leaflet, based on the observations and the appropriate conclusions, subject to the additional follow-up measures undertaken by the Marketing Authorisation Holder.

The CHMP adopted on 3 June 2004 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation, as amended.