# SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Aldara. This scientific discussion has been updated until 1 December 2001. For information on changes after this date please refer to module 8B.**

## 1. Introduction

Anogential warts are a sexually transmitted disease, with a high rate of transmission and significant psychosocial morbidity. They are caused by human papilloma virus (HPV), a small non-enveloped caspid DNA virus, which infects epithelial cells. The most common presentation is with condyloma acuminata, which are exophytic, cauliflower-like lumps. Subclinical HPV lesions (flat condylomas) may be identified by staining with acetic acid, which shows them as slightly raised shiny white (acetowhite) and rough surface. Condyloma acuminata may involve any part of the genitalia, and are commonly found on the penis, vulva, vagina, perineum, and the anus. Secondary internal involvement may occur in the cervix, urethra or rectum. In the immunocompromised patient condylomata may be particularly extensive and persistent.

It is estimated that the incidence of anogenital warts in the world is around 20 million cases per year. Transmission is mainly sexual, although vertical transmission of genital warts may occur from mother to child at birth.

No antiviral treatment is available podophyllin, which has antimitotic activity, is used though recurrence is common. Initial local removal of genital warts through chemical and surgical destruction is preferable particularly with larger condylomataand none of the local methods of treatment are entirely satisfactory. The oldest treatment. Interferon (IFN) $\alpha$, $\beta$ or $\gamma$ may be of value in the treatment of persistent anogenital warts.

Imiquimod is an immune response modifier. It is not a nucleoside analogue and its activity is believed to be principally due to induction of interferon alpha (IFN-$\alpha$), and other pro-inflammatory cytokines. Anti-viral activity and anti-tumour activity have been demonstrated in animal models.

ALDARA cream is indicated for the topical treatment of external genital and perianal warts (condyloma acuminata) in adult patients.

Imiquimod cream should be applied three times per week (every other day followed by a 2-day treatment –free interval) prior to normal sleeping hours, and should remain on the skin for 6 to 10 hours. Imiquimod cream treatment should continue until there is clearance of visible genital and perianal warts or for a maximum of 16 weeks.

## 2. Chemical, pharmaceutical and biological aspects

ALDARA is presented as a cream containing 5% w/w imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, benzyl alcohol, cetyl alcohol, stearyl alcohol, white soft paraffin, polysorbate 60, sorbitan stearate, glycerol, methyl hydroxybenzoate, propyl hydroxybenzoate, xanthan gum and purified water. The primary packaging material consists of individual heat sealed, single use sachets, each containing 250 mg of cream, containing 12.5 mg of imiquimod. The sachets are constructed from a multi-layer laminate. There is one package size of 12 sachets.

**Active substance**

Imiquimod is a heterocyclic amine. It is a white to off-white, crystalline solid that is practically insoluble in water and common organic solvents as the free base, but becomes more soluble as a salt form. Imiquimod is a relatively stable drug and is not hygroscopic.

The molecule does not possess any asymmetric carbon atoms and does not exhibit stereoisomerism. No polymorphic forms of this compound have been identified.

The free base of the active ingredient, imiquimod, is synthesised in a six-step process. The crude imiquimod produced is purified by converting it to imiquimod salt, treating with activated carbon, filtered, basified to precipitate the active which is then washed with a solvent then water and finally dried under vacuum. The in-process controls applied to the synthesis are appropriate and satisfactorily control the quality of the active drug substance.

Potential synthetic impurities have been identified and characterised. These impurities are limited individually to not more than 0.1% and in total to not more than 0.3%. The residual solvents in the drug substance are at levels far below the proposed ICH limits.

The active substance specification includes tests for appearance, identity (IR, UV), residual solvents, loss on drying, sulphated ash, heavy metals, chloride, iron, total specified and unknown related substances and assay. The analytical methods used have been validated. Batch analyses data confirm the consistency and uniformity of the active substance.

**Finished product**

**Pharmaceutical development**

The pharmaceutical development conducted by the company resulted in the production of an oil in water cream taking into consideration the physiochemical properties of the active, particularly with regard to solubility, and the requirements for penetration through the skin barrier. Temperature/solubility relationships were investigated with regard to the manufacturing and packaging processes and the ability of the oil phase to retain the active in solution.

Formulations using two preservative systems were selected for clinical trials. *In vitro* studies were conducted to demonstrate that the two formulations released imiquimod at the same rate. One of the systems was found to result in the precipitation of an insoluble salt of imiquimod and was subsequently abandoned, resulting in one formulation being taken forward in the application for marketing authorisation.

The preservative effectiveness of this product was found to rely heavily on the level of preservative in the product and reduction over time may result in observed variable efficiency of the system. However, as the finished product is packaged in single-dose sachets the preservative system was considered adequate.

**Manufacture and control**

A typical oil-in-water cream non-sterile process manufactures the cream. The two phases are prepared separately. The aqueous phase is added to the oily phase under vacuum. The emulsion is homogenised, mixed and subsequently cooled down with continuous mixing. The critical processes include temperature control, mixing times, vacuum rate, and environmental control. Additional validation data (type of emulsion, droplet size, confirmation of complete drug dissolution) were provided for the bulk and finished product and no significant differences were noted. The in-process controls applied during manufacture appear, from batch analyses data, to give a reproducible product.

With respect to other ingredients, the cream contains isostearic acid as solubiliser for the active ingredient, cetyl and stearyl alcohols as viscosity modifiers, white soft paraffin as emollient, polysorbate 60 and sorbitan stearate surfactants, benzyl alcohol as preservative and co-solvent, methyl and propyl hydroxybenzoate as preservative, glycerol as co-solvent and viscosity modifier, xanthan gum as viscosity modifier, and purified water. All the excipients, with the exception of isostearic acid and xanthan gum, comply with the requirements of Ph.Eur or B.P. Xanthan gum is controlled to USNF with an additional test for microbiological quality. An in-house monograph controls Isostearic acid.

Control tests applied on the finished product include appearance, identification (imiquimod, methyl and propyl hydroxybenzoates, benzyl alcohol), assay (imiquimod, methyl and propyl hydroxybenzoates, benzyl alcohol), degradation product, pH, viscosity, microbiological quality and minimum fill weight. The methods were satisfactorily validated and appear capable of controlling the bulk intermediate and the finished product within their specifications. Results from batch analyses showed that batches complied with release specifications.

**Stability**

The active substance has shown good stability characteristics when tested under a number of different conditions. The data provided fully support the proposed 2 year re-test period for the active substance.

For the bulk cream the shelf-life when stored below 25°C and protected from freezing is supported by data generated on 2 batches stored at 25°C over 6 months. For finished product packaged at the commercial production site in the UK, stability data are available on batches stored and tested under ICH conditions. Supplementary data covering storage during transport were presented. The results demonstrate decreases in viscosity (but within the proposed limits) with no other parameter significantly affected. Overall the data support the shelflife as defined in the SPC. Additional real time data from on-going stability studies with the product intended for marketing will be submitted when available.

In summary, the chemical and pharmaceutical documentation for imiquimod was considered to be acceptable.

## 3. Toxico-pharmacological aspects

**Pharmacodynamics**

The pharmacodynamic action of imiquimod has been studied *in vitro* and *in vivo.*

In cultured murine cells imiquimod induced cytokine secretion in a wide variety of cell types including spleen, bone marrow, liver, peritoneal exudate and alveolar macrophages. The pattern of cytokines differed between the cell types. Studies with mouse macrophages produced results consistent with a cell surface receptor for imiquimod. Further *in vitro* studies showed that imiquimod is a potent inducer of cytokines in human peripheral blood mononuclear cells (PBMC). Its two metabolites were also potent inducers. Induction occurred 1-2 hours after exposure and generally peaked after 8 hours.

In a study of the mode of action, cytokine gene expression in a human epidermal carcinoma cell line (COLO-16) and human keratinocytes following exposure to imiquimod was determined. There was both stimulation (1 μg/ml) and down-regulation (10 μg/ml) of IL-6 and IL-8 mRNA synthesis. Further experiments with keratinocytes showed that, of the 5 cytokines assayed, IL-8 was present in the supernatant whereas there was little or no effect in cultures of melanocytes or fibroblasts. In this instance, imiquimod was substantially less potent than Poly I:C (50 μg/ml).

The ability of imiquimod to stimulate cytokine production was confirmed in *in vivo* studies conducted mainly in mice (both normal and immunodeficient), but also in rats, guinea pigs and Cynomolgous monkeys. The results confirm the ability of imiquimod to stimulate cytokine production.

Antiviral activity has been examined in cell cultures and in *in vivo* animal infection models. *In vitro* imiquimod inhibited rhinovirus 1A, respiratory syncytial virus and varicella zoster virus as assessed by 50% plaque reduction in virus-infected cells. In guinea pigs a single oral dose (5 mg/kg) was effective against primary genital herpes (HSV-2) infection. Under certain conditions intravaginal imiquimod reduced latent neural HSV-2 in ganglia and also recurrences, with early or prolonged treatment being of respective importance.

In other animal infection models, imiquimod was effective against Rift Valley fever and Banzi viruses (in mice) and yellow fever virus (in Cynomolgous monkeys). With regard specifically to HPV, imiquimod administered at 5-mg/kg i.p. to mice implanted with tumours expressing the HPV 16 E7 gene reduced the weight of tumours by up to 84%.

Imiquimod was shown to be an effective anti-tumour agent in mice implanted with a number of different tumour cell types.

Imiquimod has been assessed in safety pharmacology tests both *in vitro* and *in vivo.* Although there were a number of findings in the intravenous dog study (cardiac stimulation, central nervous system stimulation and some autonomic nervous system inhibition), none of the effects found raised any safety concerns.

**Pharmacokinetics**

The pharmacokinetic profile of imiquimod was studied in rats, rabbits, and monkeys, the main species used in the preclinical program. Following oral administration imiquimod was rapidly absorbed. Following repeated dermal administration of 1 or 5 mg/kg imiquimod during a 4 week rat toxicity study, the systemic exposure to imiquimod or its metabolites was minimal. No imiquimod or metabolite was detected in the plasma of the low dose group, low doses of the metabolite S-26704 were found at 5 mg/kg (approximately 25 times the clinical dose).

Distribution studies were conducted in rats (pigmented and non-pigmented) and monkeys with radiolabelled compound administered orally. Distribution was wide and rapid in both species with higher levels in the organs of elimination (liver, kidney and gall bladder) compared to the plasma after 72 hours. In pigmented rats high concentrations were found in the skin and eye and were still high 72 hours after dosing, indicating non-specific melanin binding. In pregnant rabbits $^{14}$C-imiquimod was administered intravenously. Radiolabel was present in the uteri, placentae, amniotic fluid and foetuses. The exact distribution within the foetus as determined by whole body autoradiography has not been established.

There are relatively few animal data on metabolites. In rat urine, however, radiochromotography of untreated urine revealed 3 peaks increasing to 6-7 following hydrolysis with β-glucuronidase. The structure of the two major metabolites formed by hydroxylation, S-26704 and S-27700, was determined from human urine. They are also found in rat and monkey. Excretion is via the urinary and biliary routes.

**Toxicology**

**Single dose toxicity** of imiquimod was studied in mice, rats and monkeys. These studies indicated a high degree of safety. Adverse effects were limited to the central nervous system resulting in a number of clinical signs, usually convulsions, prior to death.

In two dermal toxicity studies in rabbits with doses of 2000 and 5000 mg/kg under occlusion there were no deaths and no signs of toxicity other than mild transient erythema at the application site.

**Repeated dose toxicity** of imiquimod after oral administration was studied in rats and monkeys up to 6 months. In both studies, the only adverse effects apart from slight effects on body weight and food consumption were considered to be the result of exaggerated pharmacological activity, i.e. hyperplasia of B- and T-cell lymphoid tissue, increased number of plasma cells, enlargement of spleen and lymph nodes, Kupffer cell hyperplasia, mononuclear/macrophage cell accumulation or proliferation. These included over-stimulation and in some animals subsequent down-regulation of lymphoid tissue. These effects were reversed during a recovery period during which animals were not dosed. There were no other target organs and a No Observed Adverse Effect Level (NOAEL) of 3mg/kg was established in both species.

Dermal toxicity studies, where imiquimod was applied three times per week, were conducted in rats (up to 4 months), and mice (up to 4 months). In rats significantly decreased body weight and increased spleen weight were observed at 0.5 and 2.5 mg/kg, and local skin irritation (severe erythema, slight to moderate oedema, desquamation and scabbing) more severe than that seen in humans was observed. Histopathological examination revealed epidermal inflammation with epidermal ulceration and hyperkeratosis. There was no good dose/response relationship and a No Observed Effect Level (NOEL) was not established. In treated mice spleen weight was increased, however, was not attributed to systemic exposure to imiquimod and its metabolites, which is negligible following dermal administration. In mice there was a better dose/response and a NOEL of 0.4 mg/kg (approximately twice the clinical exposure).

In a general reproductive performance and fertility study and teratogenicity study in rats, dams showed moderate signs of toxicity including decreased body weight gain and food consumption, tremors and/or convulsions. In pups there was decreased body weight and/or retarded ossification. There were no adverse effects on the reproductive performance of the $F_0$ generation nor any effects on the post-natal development and reproductive performance of the $F_1$ generation. In a general reproductive performance and fertility study in rabbits, the only signs of toxicity were tremors and convulsions in the dams. There were no effects on the pups.

In a standard battery of *in vitro* and *in vivo* genotoxicity tests, imiquimod lacked genotoxic potential. The carcinogenic potential of imiquimod following dermal application was assessed in mice over 18 months. Benign squamous cell tumours (including papillomas and keratocarcinomas) were detected in the skin at the application site in 4 control and 3 high dose animals. In addition, lymphosarcomas at the application site were found in one control and in high dose animals. There were no differences between control and high dose animals in the incidence of other tumours or non-neoplastic lesions.

Ocular and skin irritation studies in the rabbit were conducted with imiquimod and imiquimod cream. The results indicate that imiquimod itself is not irritant and that the cream is in general only mildly irritant.

Vaginal irritancy of 1% and 5% imiquimod creams has been assessed in rats and rabbits. In rabbits there was no vaginal irritation. In rats there was no histopathological evidence of vaginal irritation however there were monocytic infiltrates below the vaginal epithelium, increased spleen weight and lymphoid hyperplasia consistent with the pharmacological activity of the compound.

Minor differences in the formulations used in animal studies compared with the clinical formulation were adequately addressed by the applicant and are not considered to pose a problem.

**Summary and conclusion on preclinical pharmacology and toxicology**

Overall, in the primary pharmacodynamic studies Imiquimod has been shown to stimulate the production of several cytokines, in particular α interferon, from a number of different cell types. The subsequent effects on cells of the immune system result in antiviral and anti-tumour activity. There were adverse effects in safety pharmacology studies but these are of no relevance to the proposed clinical use where topical application does not result in systemic exposure.

Overall, the toxicology program indicates a high degree of safety with no target organ toxicity other than that attributed to exaggerated pharmacological activity. Imiquimod did not affect fertility and it was neither teratogenic nor genotoxic. In carcinogenicity study in mice there was no increase in the incidence of tumours or non-neoplastic lesions as the result of dermal exposure to imiquimod. This information has been included in the Summary of Products Characteristics (SPC).

## 4. Clinical aspects

The clinical program was aimed at evaluating the efficacy and safety of imiquimod cream for the topical treatment of external genital and perianal warts (condyloma acuminata) in adult patients. The core clinical documentation consisted of 16 clinical pharmacology studies, 3 phase II studies and 5 phase II/III trials.

**Pharmacodynamics and Pharmacokinetics**

The pharmacodynamic and pharmacokinetic properties of imiquimod were studied in 9 phase I trials in healthy volunteers or genital wart patients. Both oral and topical administration of imiquimod cream resulted in stimulation of cytokines, including interferon α. The data indicate that imiquimod does not have a direct anti-viral effect, but that it stimulates immune body responses to fight the viral infection. Two cumulative irritation studies, in which Aldara cream was applied using an occlusive patch system once daily for 21 days, showed that the active control was more irritating than imiquimod, and imiquimod was more irritating than vehicle.

**Pharmacokinetic profile:** Negligible absorption of imiquimod occurred after radiolabelled imiquimod was applied to the forearm of healthy volunteers in two studies and to patients with anogenital warts in one study. Urinary recovery of imiquimod after single and repeat application was <0.9% of the total dose. No quantifiable levels of (≥ 5 ng/ml) of imiquimod or its metabolites were detected in serum of patients following single or multiple topical doses.

The data defining systemic absorption of imiquimod are limited by the use of a bioanalytical method with a 5-ng/ml lower limit of quantification. Systemic exposure (percutaneous penetration) was calculated from recovery of carbon-14 from radiolabelled imiquimod in urine and faeces.

The pharmacokinetics of oral imiquimod 50 - 300 mg, and subcutaneous imiquimod 15 and 30 mg, were studied in 4 trials in 116 healthy volunteers and 16 patients with anogenital warts in one trial.

After oral administration imiquimod was rapidly absorbed. The mean $C_{max}$ after 100 mg imiquimod was 120 ± 60 ng/ml, AUC of 573 ± 301 ng.hr/ml and $t_{1/2}$ was 2.7 hours. A linear dose-concentration relationship was shown for doses in the range of 100-250 mg. Orally administered imiquimod is rapidly and extensively metabolised into two main metabolites S-26704 and S-27700. Only 0.2 – 0.6% of an oral dose was recovered as unchanged compound in the urine.

**Interactions:** Interaction studies have not been conducted with the topical formulation. This was considered acceptable, as interactions with systemic drugs would be limited by the minimal percutaneous absorption of imiquimod cream. This has been noted in section 4.5 of the SPC. A warning that there is a lack of experience with regard to concomitant use of imiquimod cream with other topical therapy is included in section 4.4 of the SPC.

**Special populations:** No alteration in dose or schedule of application of imiquimod cream has been recommended for older patients (75 years or older) or for patients with renal or hepatic impairment.

**Bioequivalence:** Three different formulations of 5% imiquimod cream were used in the clinical trial programme (development formulations – 2d & 2h and the proposed market formulation – 2e). No direct comparisons have been made amongst these three formulations. However, the pharmaceutical differences between them do not raise a serious concern relating to their safety or efficacy.

**Therapeutic efficacy**

The main therapeutic efficacy data are derived from five controlled phase II/III trials carried out in a total of 1031 patients. Of the 1031 patients, 421 patients were treated with imiquimod cream 5%, 192 with 1%, and 418 received vehicles only. In addition, three open phase II studies in 94 male patients provided the basis for the dosing regimen used in the pivotal studies.

**Open pilot studies:** Two open pilot phase II studies (004 and 005), in male patients, indicated that both 1% and 5% imiquimod cream applied for 24 hours, three times weekly and once daily, caused a reduction in the wart area and in wart number but the wart area tended to increase when the treatment was stopped. The frequency of application, whether three times weekly or daily, did not appear to have particular impact. The third open pilot study in uncircumcised male patients (study 1147) enrolled insufficient numbers of patients and was discontinued.

**Double blind, controlled studies:** One phase II trial and four phase III trials were randomised, double blind, parallel group and vehicle controlled.

| Study | Formulation (Imiquimod %/Vehicle) | | | Age Range(years) [mean ± SD] | Male/Female |
|---|---|---|---|---|---|
| | 5% | 1% | vehicle | | |
| **Phase II** | | | | | |
| R-837T-017 | 51 | - | 57 | 18-69 [30 ± 9] | 98/10 |
| **Phase III** | | | | | |
| 1004-IMIQ | 109 | 102 | 100 | 18-70 [31 ± 11] | 180/131 |
| 1005-IMIQ | 94 | 90 | 95 | 18-62 [31 ± 10] | 154/125 |
| 1109-IMIQ | 94 | - | 101 | 18-71 [33 ± 9] | 195/0 |
| 1110-IMIQ | 73 | - | 65 | 17-73 [27 ± 11] | 0/138 |

**Patient population:** Treated or untreated males and non-pregnant and non-lactating female patients over the age of 18 were included. In the phase III trials, patients were required to have 2 to 50 warts at study entry prior to biopsy and have a minimum post-biopsy wart area of 10 $mm^2$. Studies 1109 and 1110 also defined a maximum wart area of 2000 $mm^2$ post-biopsy. All patients had negative HIV tests. Patients who had previously received imiquimod, interferon or interferon inducers, oral or topical anti viral therapy were excluded, as were patients with rectal, urethral, cervical, or vaginal warts.

The genital/perianal warts were diagnosed by clinical inspection, which was confirmed by biopsy for the phase III trials. The histology of the biopsy had to be suggestive of or diagnostic of HPV infection for inclusion. In addition, *in situ* hybridisation for HPV typing was conducted on biopsies from two of the trials.

**Dose regimens:** Three of the five controlled studies had two groups of patients who received either 5% imiquimod cream or vehicle only (017, 1109, 1110). In the two other studies (1004 and 1005) a third group of patients were treated with 1% imiquimod cream in order to allow the assessment of dose response. In all studies imiquimod was given three times per week except in study 1005, where it was given every day. The cream was applied for 8 hours a day in all studies except for study 017 where it was retained for 24 hours.

**Efficacy parameters:** The primary efficacy criteria were the total clearance of all visible baseline/target warts during the treatment period. Patients who had total wart clearance during the treatment period were assessed for recurrence of baseline/target warts during a 12-week treatment-free follow-up period. Secondary endpoints included partial clearance, as defined by a > 50% reduction in baseline wart area. Both ITT and per protocol analyses were presented. Recurrence rates were calculated using withdrawals excluded analysis.

**Efficacy results:**

**Total clearance rates:** The phase II trial showed that 5%imiquimod cream was significantly better than vehicle alone in producing total wart clearance. The median time to total clearance was 7 weeks in the imiquimod group. There were no patients with total wart clearance in the vehicle group.

The results of the 4 phase III efficacy studies show that 5% imiquimod was significantly more effective than vehicle, with intent-to-treat total wart clearance rates of 15-52% in the imiquimod group as opposed to 3-18% in the vehicle group. The median time to total clearance of the genital warts ranged from 7-12 weeks in the imiquimod group and 8-13 weeks in the vehicle treated group. In the two studies that included the 1% strength, the 5% formulation was found to be significantly more effective than the 1%, with intent-to-treat total clearance rates of 50% and 52% versus 21% and 14% respectively.

**Partial clearance rates:** Partial clearance rates as defined by >50% reduction in the baseline wart area, were significantly higher in the 5% imiquimod group than the vehicle treated group. The intent-to-treat partial clearance rates ranged between 46-81% in the imiquimod group as compared with 10-45% in the vehicle treated group. The partial clearance rates in the group treated with 1% imiquimod were considerably lower, at 35-37%, than the 5% group.

The intent-to-treat total rate of clearance in study 1109, which included only male patients was lower (15% imiquimod, 4% vehicle) than the other studies, which included female patients. In two (1004, 1005) of the three trials which included both male and female patients (017, 1004, 1005) the total and partial clearance rates were higher in the females. This may be due to the different keratinisation and moisture content of the lesions. However, it is also possible that these differences are due to a lower spontaneous clearance in the males treated with vehicle alone compared to the females. The total and partial clearance rates with 5% imiquimod in male patients, although lower than those in females, remains significantly higher than those in the vehicle treated group.

**Recurrence rates:** The recurrence rates were defined as the percentage of patients whose anogenital warts recurred during the follow-up period, having completely cleared during the treatment period. The patients who withdrew during the follow-up period were excluded from the analysis in order to avoid a spuriously low recurrence rate. The recurrence rates were consistently higher in the imiquimod group than in the vehicle group, although these differences were not statistically significant. There is sufficient evidence to suggest, however, that clinical benefit over the 16 week treatment period and the short period of follow-up is greater than that with vehicle alone. The follow-up period of 12 weeks may be too short to demonstrate the true recurrence rates in the treatment of anogenital warts, since up to 70% of warts recur within a year regardless of the treatment.

All trials excluded patients who had been previously treated with imiquimod, there are therefore no data to assess the value of the repeat application of imiquimod in treatment of recurrence of anogenital warts.

**Dosing schedule and duration of application:** The 5% imiquimod cream produced greater total clearance of anogenital warts regardless of whether it was given three times weekly or on a daily basis. The safety profile of the two regimens, however favored the three times weekly regimen.

Similarly, the efficacy of 5% imiquimod was the same whether it was left on the application site for 8 hours or 24 hours. However it was considered much more practical to apply cream only for the normal duration of sleep, i.e. 8 ± 2 hours.

**Efficacy in immune deficient patients:** Sufficient data to support the efficacy of imiquimod in HIV patients has not been provided. A warning has been added to indicate this in section 4.4 of the SPC.

**Combination with other therapies:** No studies to examine the effect of combining imiquimod with other therapies used for the treatment of anogenital warts, such as surgical removal, cryotherapy, podophyllin, or trichloroacetic acid have been carried out. Two studies examined the safety of topical imiquimod following wart ablation by electrocauterisation (24 patients) and by cryotherapy (18 patients). There were no differences in median time to wound healing or in the incidence of reported adverse reactions after cryotherapy and imiquimod compared with cryotherapy and vehicle. The adverse reactions were significantly higher in the imiquimod group after electrocauterisation compared to the vehicle treated group.

**Summary and conclusions on efficacy:**

There is sufficient evidence that imiquimod 5% cream given three times weekly for 8 hours a day is superior to both vehicle and 1% imiquimod cream both in terms of total and partial clearance of the anogenital warts. Imiquimod 5% cream appears to have a greater benefit in females as compared to males. However, there is sufficient evidence to show that imiquimod does have some benefit in men.

The follow-up period in the efficacy studies was not long enough to ascertain whether the recurrence rate after treatment with imiquimod is lower than existing therapies. There is no efficacy or safety data to assess the value of repeat applications of imiquimod in recurrent anogenital warts. The duration of application is limited to 16 weeks.

Sufficient data to support the efficacy of imiquimod in HIV patients has not been provided. However, it is recognised that HIV positive patients respond less well to other therapies for warts as well.

**Safety**

The safety database for imiquimod was derived from 1031 patients in five phase II/III studies and 709 patients in phase I/II trials. All patients had anogenital warts. Safety data from a small pilot study in HIV positive patients has also been presented. A total of 980 patients or subjects were exposed to imiquimod 5% and 250 patients or subjects exposed to imiquimod 1% cream. In the controlled clinical trials, 412 patients received imiquimod (1% and 5%) three times weekly and 176 patients received it once daily. There is no safety data for the use of imiquimod beyond 16 weeks, i.e. a single treatment cycle. Ten patients became pregnant during the trials.

In the clinical programme there was one death during or shortly after treatment with imiquimod. The cause of death was overdose with methamphetamine and fluoxetine hydrochloride and it was considered to be unrelated to imiquimod.

In clinical trials, 13 patients treated with imiquimod and 4 patients treated with vehicle suffered a serious adverse experience. All apart from one case of stricturing of the foreskin, were not thought to be related to the study drug.

In the 21 completed trials with topically applied imiquimod, 21 % (359/1740) withdrew from the trial. Only 1.8% (31/1740) of these discontinued due to adverse events: 17 for local skin reactions, 9 for other adverse events (including the one death) and 5 for laboratory abnormalities.

In controlled trials the most commonly reported adverse events were local skin reactions. Remote skin reactions, mainly erythema, were also reported in these trials. These reactions were at non-wart sites, which may have been in contact with imiquimod cream. Most skin reactions were mild to moderate in severity and resolved within 2 weeks of treatment cessation.

In the trials with three times a week dosing, the most frequently reported adverse drug reactions judged to be possibly or probably related to imiquimod cream treatment were application site reactions

at the wart treatment site, reported by up to 79% of patients. Some systemic adverse reactions, including headache, flu-like symptoms, and myalgia were also reported by imiquimod and vehicle treated patients.

| **Adverse reaction** | **Females** | | **Males** | |
|---|---|---|---|---|
| *Application Site Reactions:* | | | | |
| Itching | 32% | 20% | 22% | 10% |
| Burning | 26% | 12% | 9% | 5% |
| Pain | 8% | 2% | 2% | 1% |
| *Systemic Reactions:* | | | | |
| Headache | 4% | 3% | 5% | 2% |
| Influenza-like symptoms | 3% | 2% | 1% | 0% |
| Myalgia | 1% | 0% | 1% | 1% |

Other adverse events that were specifically examined included depression in view of the single case of death due to methamphetamine overdose and the known association of interferon and depression, even though very little imiquimod is absorbed after topical application. Depression occurred in 13 patients in the whole clinical programme (1740 patients). Most of these cases were attributed to pre-existing depression (5) or to intercurrent illness (8). One case was thought to be possibly related to therapy.

No abnormal trends in routine laboratory test data were noted (biochemistry with liver function tests, haematology). Leucopenia was associated with oral administration of imiquimod. Statistically significant decreases in neutrophils, absolute neutrophils and basophils at the end of treatment as compared with baseline were seen with topical use of imiquimod 5% cream. However, there were no consistent trends and these changes did not appear to be clinically significant.

**Elderly patients:** The safety data with imiquimod cream in patients older than 65 years of age are limited to 4 patients. However, as the number of elderly patients using imiquimod is likely to be low, the lack of data is accepted. A warning that there is limited experience in patients older than 65 years of age has been included in section 4.4 of the SPC.

**Pregnant patients:** Ten patients who had received imiquimod became pregnant during clinical trials. Of these, 1 patient miscarried, 4 chose to terminate, 2 were lost to follow-up and 3 delivered healthy full term babies.

**Uncircumcised males:** Although uncircumcised males were at no point excluded from studies, the majority of males recruited were circumcised. The safety database in uncircumcised men with foreskin-associated warts treated with imiquimod cream three times weekly, who were retracting the foreskin and washing the area daily, is less than 100 patients. In other studies, in which a daily foreskin hygiene routine was not followed, there were two cases of severe phimosis and one case of stricture leading to circumcision.

The company is currently carrying out studies to fully profile the effect of imiquimod in uncircumcised patients. Until further data is available, a warning that imiquimod cream for the treatment of uncircumcised men with foreskin-associated warts is not recommended unless the benefit is felt to outweigh the risk has been included in section 4.4 of the SPC. Furthermore, stricture of the foreskin is clearly described.

**HIV Positive Patients:** The safety data in topically treated HIV positive patients is limited to 62 males and 3 females. Application site reactions, diarrhoea and herpes simplex were the commonest adverse events. Although the incidence of these adverse events was considerably higher in the imiquimod treated group, these differences were not statistically significant.

**Patients with renal and hepatic impairment:** There are no data with the use of imiquimod in patients with renal or hepatic impairment. However as the systemic absorption of imiquimod after topical application is negligible, this is not likely to be clinically important.

**Summary and conclusions on clinical safety:**

Imiquimod cream appears to be associated with a significant number of adverse events, mainly consisting of local skin reactions. Other adverse events reported were flu-like symptoms and fungal infections. In uncircumcised male patients with warts under the foreskin, the safety data, although

limited, shows that the likelihood of local skin reactions, including stricture of the foreskin requiring circumcision, is sufficiently high to warrant concern. This has been highlighted in section 4.4 of the SPC.

Adequate evidence of the safety of imiquimod in elderly patients has not been provided and this information has been included in the SPC. The safety data are limited in HIV positive patients.

**Overall Risk / Benefit analysis**

Imiquimod cream appears to be an effective therapy for the treatment of anogenital warts. The safety profile in circumcised male patients and in female patients appears to be acceptable. It is used as an outpatient treatment applied by the patients themselves. Most of the therapies currently available are painful and may require local and sometimes regional or general anaesthesia depending upon the extent of the warts. They also require trained medical staff to perform the treatment. Imiquimod cream offers an alternative to currently available treatment for anogenital warts in circumcised males and females.

For uncircumcised male patients with warts under the foreskin a warning that treatment in this patient population is not recommended unless the benefit is felt to outweigh the risk has been included in section 4.4 of the SPC until further safety data are presented. The importance of a daily foreskin hygiene routine when imiquimod is used in this patient population has also been noted. As repeat treatment with imiquimod cream after recurrence of warts has not been studied, a warning that repeats treatment with imiquimod cream is not recommended has been included in section 4.4 of the SPC.

To further establish the benefit to risk balance with reference to current therapy the CPMP discussed whether a comparator study with podophyllotoxin should be undertaken. The CPMP agreed that a comparator trial would not be pursued in this case due to practical difficulties in conducting a blinded clinical trial. Additionally there would be problems because the comparator (podophyllotoxin) has different topical formulations and different dosage regimens registered throughout the EU.

## 5. Conclusion

The quality of ALDARA cream, as demonstrated in the chemical and pharmaceutical documentation, is considered acceptable.

Based on preclinical pharmacodynamic studies, both oral and topical administration of imiquimod produce an increase in interferon and other cytokines, as well as CD4 TH1 markers. In animal models imiquimod is effective against viral infections and acts as an antitumor agent principally by induction of alpha interferon and other cytokines. It appears that while imiquimod does not have a direct anti-viral activity, it stimulates body responses which help fight the viral infection..

ALDARA 5% cream given three times weekly has demonstrated statistical superiority in efficacy, when compared to vehicle (placebo), in treating external genital and/or perianal warts. The safety concern of foreskin stricture in uncircumcised males and the concern that repeat treatment with imiquimod cream has not been studied have been adequately addressed with the inclusion of warnings in section 4.4 of the SPC. Therefore, the CPMP considered the benefit to risk assessment positive and recommended the granting of a Marketing Authorisation for this medicinal product.