EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zyclara

imiquimod

Procedure No. **EMEA/H/C/002387**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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List of abbreviations

CHMP: Committee for Medicinal Products for Human Use

EMA: European medicines agency

GCP: Good Clinical Practice

ERA: Environmental Risk Assessment

MA: Marketing Authorisation

MAH: Marketing authorisation holder

SmPC: Summary of product characteristics

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Meda AB submitted on 22 June 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zyclara, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Hybrid of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 July 2010.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: topical treatment of clinically typical, visible or palpable actinic keratoses (AK) of the full face or balding scalp in adults.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and appropriate clinical data.

Information on paediatric requirements

Not applicable

Information on the reference medicinal product

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Aldara 5% cream
- Marketing authorisation holder: MEDA AB, Solna, Sweeden
- Date of authorisation: 18/09/1998
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/98/080/001-002

Licensing status

Zyclara has been given a Marketing Authorisation in the United States and Canada on 29/03/2010 and 05/01/2010 respectively.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Robert James Hemmings

- The application was received by the EMA on 22 June 2011.
- The procedure started on 20 July 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 October 2011.
- During the meeting on 17 November 2011 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 November 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 March 2012.
- During the CHMP meeting on 19 April 2012 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 May 2012.
- During the meeting on 20 June 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zyclara on 21 June 2012.

2. Scientific discussion

2.1. Introduction

The Marketing Authorisation application for Zyclara, 3.75% cream, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The proposed product differs from the reference product, Aldara 5% cream, in therapeutic indication and strength. These differences, together with the fact that the pharmaceutical form is a topical cream, make it necessary to carry out new clinical studies as bioequivalence cannot be demonstrated through bioavailability studies.

Imiquimod is an immune response modifier. Saturable binding studies suggest that a membrane receptor for imiquimod exists on responding immune cells. Imiquimod has no direct antiviral activity. In animal models imiquimod is effective against viral infections and acts as an antitumour agent principally by induction of alpha interferon and other cytokines. The induction of alpha interferon and other cytokines following imiquimod cream application to genital wart tissue has also been demonstrated in clinical studies. Increases in systemic levels of alpha interferon and other cytokines following topical application of imiquimod were demonstrated in a pharmacokinetic study.

These statements have received further support in the last years [Schön & Schön 2007, Schön & Schön 2008]. It may now be considered as established that the so-called toll-like receptors (TLR) 7 and 8 are the main targets of imiquimod. Imiquimod as the lead compound of the imidazoquinolines yields a TLR7/8-mediated activation of the central transcription factor nuclear factor-kappaB (nfκB), which leads to induction of proinflammatory cytokines and other mediators. Cutaneous dendritic cells are the primary responsive cell type and initiate a strong T-helper-cell (Th1) weighted antitumoural cellular immune response. Recent research has shown that dendritic cells themselves acquire direct antitumoural activity upon stimulation by imiquimod. In addition, there are a number of secondary effects on the molecular and cellular level that can be explained through the activation of TLR7/8. The

proinflammatory activity of imiquimod, but not resiquimod, appears to be augmented by suppression of a regulatory mechanism, which normally limits inflammatory responses. This is achieved independently of TLR7/8 through interference with adenosine receptor signalling pathways. Finally, at higher concentrations imiquimod exerts Bcl-2- and caspase-dependent proapoptotic activity against tumour cells.

The proposed indication for Zyclara 3.75% (imiquimod) cream is different from the reference product and includes topical treatment of clinically typical, nonhyperkeratotic, nonhyperpertrophic, visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults. During assessment, and due to absence of active controlled studies, this indication was limited to second line treatment being the approved indication: Topical treatment of clinically typical, nonhyperkeratotic, nonhyperpertrophic, visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults, when other topical treatment options are contraindicated or less appropriate.

The recommended dose per application is up to 2 sachets, containing 9.375 mg imiquimod in 250 mg cream (3.75%) each, once daily before bedtime to the skin of the affected area for two treatment cycles of 2 weeks each separated by a 2-week no-treatment cycle or as directed by the physician. The cream should remain on the skin for approximately 8 hours. The product is not to be used in children/ adolescents below 18 years of age as no data are available. The prescriber should demonstrate the proper application technique to the patient to maximize the benefit of Zyclara cream therapy.

The active substance, imiquimod, has well established safety and efficacy and has been on the market since 1998 as 5% cream.

2.2. Quality aspects

2.2.1. Introduction

Zyclara is a white to faintly yellow topical cream base, formulated as oil-in-water vanishing cream base. Is packaged in a form, fill and seal multi-layer laminate single dose sachet. Each sachet contains 250 mg of imiquimod 3.75% topical cream. The pack sizes include 14, 28 and 56 sachets.

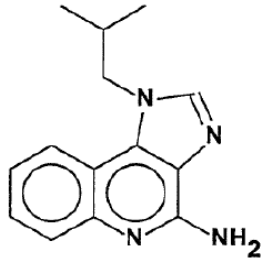
2.2.2. Active substance

The active substance is imiquimod, chemical name 1-(2-Methylpropyl)-1H-imidazo [4,5-c] quinolin-4-amine; 4-Amino-1-isobutyl-1H-imidazo [4,5-c] quinolone. The corresponding molecular formula is C14H16N4. The molecule does not contain any chiral centres and no polymorphic forms.

Imiquimod is not described in any pharmacopoeial monograph.

It is an odourless, white to off-white crystalline solid, practically insoluble in water and common organic solvents as free base, but becomes soluble as a salt form. Its solubility decreases with increasing pH.

Imiquimod has the following structural formula:



Manufacture

Imiquimod is synthesised according to the same process currently approved for use in Aldara 5% Cream. It is synthesized in six main steps, including a purification step, using well defined starting materials.

Stability data have been provided for 6 batches of the drug substance and the result support the proposed retest period of 2 years when stored below 30 °C in double polyethylene bags in cardboard kegs.

Adequate in-process controls are applied at each stage of the synthesis. In general, the specifications and control methods for intermediate products, starting materials and reagents have been presented.

Batch analysis data are provided on 3 batches produced with the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly.

Specification

The drug substance specification as tested by the active substance manufacturer is identical to that currently approved for imiquimod used in the reference product.

As there is no monograph of imiquimod in the Ph.Eur., the applicant developed its own specification and test methods for the quality control. Control tests include appearance, identification, loss on drying, heavy metals, residue on ignition, chloride residue, iron content, platinum content, assay on dried basis, purity and residual solvents.

At the time of the CHMP Opinion the analytical methods used were not fully validated. For this reason the CHMP issued a recommendation to the applicant to complete the validation of these analytical methods. However this raises no concern about the safety of the active substance as the results of batch analysis comply with the specification.

The limits set for specification parameters are acceptable and in line with batch results, stability studies and CHMP/ICH guidelines. The analytical methods used are sufficiently described and fully validated in line with the CHMP/ICH requirements.

The acceptance criteria for impurities, including limits for organic impurities, inorganic impurities and residual solvents, are defined. The limits were evaluated and found to be acceptable from the point of view of safety. No genotoxic impurities were detected in the batches of the active substance. No solvents are carried over from early steps of the synthesis.

Results of analysis of three batches of the active substance were provided. Compliance with the specification was demonstrated.

Stability

Stability data of one batch of the active substance up to 60 months and of several batches up to 24 months of storage at 25°C/60% relative humidity (RH) and 6 months at 40°C/75% RH were provided. The stability parameters measured include UV assay, HPLC assay, LOD and HPLC purity.

The stability data support the proposed retest period of 2 years when stored in double polyethylene bags in a cardboard keg as secondary packaging.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim was to develop an imiquimod cream formulation at lower concentrations using the same excipients as the currently marketed Aldara 5% cream, with emphasis on physical and chemical stability, imiquimod solubility, similar emollient properties and dose proportionate imiquimod delivery. This lower strength optimized formulation would be used daily, for a much shorter therapy regimen and with less potential side effects.

Zyclara 3.75% cream contains the same active ingredient and excipients which are of the same quality as that of Aldara Cream 5%. The quantity of the excipients in both formulations is identical with the exception of the following changes to the proposed formulation when compared to Aldara:

- A reduction in the level of the active substance
- A reduction in the level of isostearic acid
- A corresponding gain in purified water

This change in the formulation is considered acceptable for the development of a lower strength formulation.

At the time of the CHMP Opinion the analytical method used for controlling one of the excipients was not fully validated. For this reason the CHMP issued a recommendation to the applicant to complete the validation of this analytical method. However this raises no concern about the safety of the finished product as the results of batch analysis comply with the specification.

Adventitious agents

Not applicable

Manufacture of the product

The manufacturing process for Zyclara is essentially the same as that of the reference product Aldara. It uses standard pharmaceutical techniques for topical creams i.e. dissolution, mixing and heating of imiquimod in the oily phase and dissolution of the preservative in the aqueous phase followed by mixing both phases.

The manufacturing process has been satisfactorily validated with respect to bulk cream manufacture, filling and sachet assembly for three validation batches.

The batch analysis data show that this medicinal product can be manufactured reproducibly according to the agreed finished product specification

Product specification

The product specifications include methods for appearance (visual), identification (HPLC, IV), assay (HPLC), drug related impurities (HPLC), pH, viscosity, minimum fill weight and microbial purity (Ph Eur).

The finished product specifications have been justified and all methods of analysis have been described and adequately validated.

Stability of the product

Stability data were provided on 3 batches of the finished products packed in sachets as intended for marketing. The batches were manufactured at the proposed site to the proposed formulation and manufacturing process. The stability studies included 36 months at long term conditions (25°C ± 2°C/60% RH ± 5°C) and 6 months under accelerated conditions (40°C ± 2°C/75% RH ± 5°C). The parameters tested the same as those for release of the finished product.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The active substance imiquimod is well known and has been in the market since 1998. The manufacturing process has essentially been the same since then and both active substance and finished product manufacturing processes are well controlled.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

The CHMP has issued two recommendations to the company. One regarding the finalisation of validation of the analytical methods of the drug substance specification. The second one refers to the finalisation of the validation of an analytical method for controlling one of the excipients of the finished product. These two issues raise no concerns as batch analysis data for the drug substance and the finished product comply with specification.

2.3. Non-clinical aspects

2.3.1. Introduction

Since the applicant (MEDA AB) of Zyclara is the same as the Marketing Authorisation Holder of the reference medicinal product centrally authorised, Aldara, the same non-clinical data was made available. .
The non-clinical aspects of Zyclara SmPC are in line with the SmPC of the reference product, Aldara. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required. The following sections summarise the available non-clinical information from the dossier of the reference medicinal product.

2.3.2. Pharmacology

Primary pharmacodynamic studies

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.

Secondary pharmacodynamic studies

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.

Safety pharmacology programme

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.

2.3.3. 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.

2.3.4. Toxicology

Single dose toxicity

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.

Repeat dose toxicity

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 3 mg/kg was established in both species.

In light of the potential for increases in systemic exposure, the CHMP requested the Applicant to discuss the available animal PK data with respect to the measured pharmacokinetic parameters in the pivotal clinical trial. In response, the Applicant has provided the following data and safety margin calculations at the no observable adverse effect level (NOAEL).

Table 1: PK data for imiquimod 3.75% and calculated safety margins

Study/ Species /	Study Duration [weeks]	Admini. Route	Therap.Dose / NOAEL [mg/kg]	C_{max} [ng/ml] Mean (min.-max.)	Safety Margin (C_{max})	AUC_{0-24h} [ng·hr/ml] Mean (min.-max.)	Safety Margin (AUC)	Ref.
Therapy / Human /	3	Dermal	0.31[1)]	0.323 (0.069-0.588)	-	5.974 (1.139-11.800)	-	1
Pharmaco-kinetik / Monkey /	Single dose	Oral Capsule	2.00	17 (6.6-23.0)	53	76 (30.0-97.0)	13	2
Repeat-Dose Tox./ Rat /	26	Oral Gavage	3.00	4.0 (1.3-7.7)	12	-	-	3
Repeat-Dose Tox./ Monkey /	26	Oral Gavage	3.00	33.1 (13.0-70.0)	102	130.4[2)] (65.0-329.0)	22	4

[1)] Therapeutic daily dose: 2 packets with 250 mg Zyclara (imiqimod) cream, 3.75% each, corresponding to 18.75 mg imiquimod / patient = 0.31 mg/kg bodyweight (60 kg person).
[2)] AUC_{0-8h} [ng·hr/ml]

Genotoxicity

In a standard battery of in vitro and in vivo genotoxicity tests, imiquimod lacked genotoxic potential.

Carcinogenicity

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.

Reproduction toxicity

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 F0 generation nor any effects on

the post-natal development and reproductive performance of the F1 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.

Local tolerance

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).

Other toxicity studies

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.

2.3.5. Ecotoxicity/environmental risk assessment

Currently, the reference product is the only imiquimod-containing product on the market in Europe and the Applicant is the sole MAH for imiquimod products. Aldara is supplied in packs of 250 mg cream, one of which may be applied for each treatment.

- For genital warts, Aldara is applied 3 times a week for up to 16 weeks.
- For small basal cell carcinomas, the cream is applied 5 times a week for 6 weeks.
- For actinic keratoses, it is applied three times a week, for one or two four-week courses, with four weeks between courses.

Zyclara (imiquimod) Cream 3.75% is supplied in single-use sachets. Patients should be prescribed no more than 56 sachets for the total 2-cycle treatment course. Up to 2 sachets (500 mg cream) may be applied to the treatment area at each application (corresponding to 18.75 mg imiquimod).

As there are no other MAHs for imiquimod-containing products, the Applicant argues that the recent sales figures for Aldara represent the total use of the active substance in Europe. The applicant argues further that because no new indications are being sought, there should be no increase in the medical use of the active ingredient and thus no change to the market penetration is expected.

Table 2: Summary of main study results

Substance (INN/Invented Name): Imiquimod			
CAS-number (if available):			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD117	2.19	Not potential PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0048	µg/L	Below 0.01 threshold
Other concerns (e.g. chemical class)			N

2.3.6. Discussion on non-clinical aspects

Non-clinical data from the reference product dossier revealed no special hazard for humans based on conventional studies of safety pharmacology, mutagenicity and teratogenicity.

The concentration of active ingredient in the proposed product is lower than that in the reference product and there is no reason to assume that the former will present more of a toxic risk than the latter. It is also accepted that there are no concerns in respect of the excipients. The impurities comply with the Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99) and none require toxicological qualification. No discussion has been provided on the potential for substances leaching from the packaging into the product. However, the multi-layer laminate used for imiquimod 3.75% cream is identical to the laminate approved for Aldara® 5% cream. For the inner layer of the sachet foil, a statement of compliance with European Directive 90/128/EEC is included hence there are no toxicological concerns.

In light of the potential for increases systemic exposure, the CHMP requested the Applicant to discuss the available animal PK data that explore the safety of the measured mean C_{max} (0.323±0.159 ng/ml and total exposure (AUC $_{0-24}$ = 5.964 g hr/ml) for imiquimod in treated patients at the end (day 21) of the PK trial (GW01-0706). In response, the Applicant has provided data from repeat-dose toxicity studies in rats and monkeys and has calculated safety margins at the no observable adverse effect level (NOAEL). The calculated safety margins (between 12 and 102, refer to Table 1) were considered satisfactory by the CHMP.

Further to the CHMP request, the Applicant has provided three separate calculations of the $PEC_{sufacewater}$ for imiquimod, all of which are below the action limit and hence indicate that there will be no risk to the environment, and that further work is not necessary. The CHMP considers that the original ERA submitted based on actual sales figures is likely to provide the most realistic estimate of the $PEC_{sufacewater}$. This figure was corroborated by the use of independently published figures on the amount of imiquimod sold. A third calculation, using yet another mean of deriving the $PEC_{sufacewater}$, also led to the same conclusion.

2.3.7. Conclusion on the non-clinical aspects

The CHMP accepts the Applicant's view that no new non-clinical studies are required. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study number	N enr.	Treatments	Brief study description / comments
GW01-0702 [R3]	242	Up to two sachets applied to the entire face or balding scalp 2.5% IMIQ QD, or 3.75% IMIQ QD, or vehicle QD for two 2-week treatment cycles	Phase 3 study of the 2-week treatment cycle regimen (2 weeks on treatment, 2 weeks of no treatment, followed by 2 weeks on treatment). Primary endpoint: complete clearance at 8 weeks after treatment (Week 14; End of Study, EOS)
GW01-0703 [R4]	240	Up to two sachets applied to the entire face or balding scalp 2.5% IMIQ QD, or 3.75% IMIQ QD, or vehicle QD for two 3-week treatment cycles	Phase 3 study of the 3-week treatment cycle regimen (3 weeks on treatment, 3 weeks of no treatment, followed by 3 weeks on treatment). Primary endpoint: complete clearance at 8 weeks after treatment (Week 17; EOS)
GW01-0704 [R5]	237	Same treatments as Study GW01-0702	Duplicate of study GW01-0702 conducted at different study centers.
GW01-0705 [R6]	250	Same treatments as Study GW01-0703	Duplicate of study GW01-0703 conducted at different study centers.
GW01-0706 [R1]	19	Two sachets applied to the entire face or balding scalp 3.75% IMIQ QD for 3 weeks	Pharmacokinetic study conducted under maximal use conditions in AK subjects. Study designed to demonstrate steady-state conditions.
GW01-0803 [R7]	179	No treatment (long-term follow-up of AK recurrence)	Observational study of subjects who are completely clear at the End of Study visit in the four Phase 3 studies (GW01-0702, GW01-0703, GW01-0704 and GW01-0705).
GW01-0901 [R8]	247	Same treatments as Study GW01-0702, without 2.5%.	Randomised, double-blind, vehicle-controlled, multicenter study. Initially, all patients received cryosurgery for 5-14 lesions, the remaining (at least) 5 lesions were then treated with study medication. Endpoint: 20 weeks after EOT.

The indication claimed by the applicant is:

Imiquimod cream is indicated for the topical treatment of clinically typical, visible or palpable actinic keratoses (AK) of the full face or balding scalp in adults.

Due to the absence of active-controlled trials, the indication as adopted by the CHMP is:

Zyclara is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhyperpertrophic, visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults, when other topical treatment options are contraindicated or less appropriate.

2.4.2. Pharmacokinetics

The pharmacokinetic program was designed to support the use of 3.75% imiquimod cream in patients with actinic keratoses when the cream is applied on a daily basis. The pharmacokinetics of the imiquimod cream, as a 5% formulation, have been studied previously in patients with both actinic keratoses and external genital warts, but never when applied at a daily frequency. Study GW01-0706 was designed to characterise the serum level profile and pharmacokinetics of daily topical applications of 3.75% imiquimod cream under maximal use conditions. Serum concentrations of imiquimod and 2 alkyl hydroxylated metabolites, S-26704 and S-27700 were measured for evaluation of studied AK patients with a disease severity towards the upper end of the proposed indication using the maximal dosing regimen (two sachets once daily for three weeks), and applied to the body surface areas that are consistent with the patients studied in the Phase 3 clinical studies (entire face or balding scalp).

Study GW01-0706 was an open label, single centre, non-randomised pharmacokinetic (PK) study in adult patients with actinic keratoses (AKs), and it is the only pharmacokinetic study included in this application that utilised the to-be-marketed 3.75% imiquimod cream formulation. The study was designed to quantify the pharmacokinetic profile of imiquimod and its metabolites following 3 weeks (21 days) of daily applications of 3.75% imiquimod cream in adult patients with actinic keratoses (AKs). The study was conducted under maximal use conditions (dose, duration, disease severity, and application areas) in a population that had at least 10 AK lesions in the application area. The application area was the entire face (exclusive of nares, vermilion, periocular areas and ears) and/or the entire balding scalp; areas estimated as approximately 200 cm^2, each. If the area of the entire balding scalp was less than 200 cm^2, the forehead area was included in order for the entire treatment area to be approximately 200 cm^2. The daily dose was 2 sachets of 3.75% imiquimod cream applied to the relevant treatment area once daily for three continuous weeks (21 Days).

Patients stayed at the study centre overnight at treatment initiation (Day 1, 1st dose), and end of treatment (Day 21, last dose) visits for collection of a 24-hour serum PK profile. During the domiciled periods of initiation (Day 1), and end of treatment (Day 20-21) visits, serum PK samples were collected predose and at planned time points through 24 hours post dose. At the end of treatment (Day 21), additional PK samples were taken at approximately 48 and 72 hours post application. Single serum samples for PK analyses of trough concentrations were obtained at Day 7 and Day 14 (in the morning prior to dosing).

Adverse events, study medication accountability, and dosing compliance were reviewed at each visit. Routine clinical laboratory assessments (serum chemistry, haematology and urinalysis) were performed at Screening, Day 1 (predose), and the end of study visits.

At total of 19 patients (14 males and 5 females) with at least 10 actinic keratoses (AKs) on the face and/or balding scalp participated in the trial, and 18 patients completed treatment. One patient discontinued prematurely due to an adverse event, and one patient missed a dose on Day 20 and was therefore excluded from the evaluation of Day 21 data.

Serum concentrations of imiquimod (R-837) were relatively low in patients treated with daily applications of imiquimod 3.75% cream for up to 21 days. While serum concentrations of two imiquimod metabolites (S-26704 and S-27700 combined) were measured throughout the study, very few samples had concentrations above the lower limit of quantitation (LLOQ). Therefore, these data were too sparse to assess. The single-dose and steady-state pharmacokinetics of imiquimod are summarised in the following table.

Table 3: Single-dose and Steady-state Pharmacokinetics of 3.75% Imiquimod Cream (Study GW01-0706)

	Mean (SD)			
Parameter	N [c]	Day 1	N [d]	Day 21
C_{max} (ng/mL)	17	0.136 (0.059)	17	0.323 (0.159)
C_{min} (ng/mL) [a]	–	NA	17	0.199 (0.109)
T_{max} (hr) [b]	17	9.0 (4.0-24.03)	17	9.0 (4.0-16.0)
AUC_{0-24} (ng•hr/mL)	17	1.831 (0.889)	17	5.974 (3.088)
AUC_{0-t} (ng•hr/mL)	17	1.679 (1.056)	–	NA
AUC_{0-inf} (ng•hr/mL)	11	4.443 (1.309)	–	NA
λ_z (1/hr)	11	0.0450 (0.0219)	15	0.0294 (0.0142)
$T_{½}$ (hr)	10	19.818 (10.125)	15	29.260 (16.979)
R_{AUC}	–	NA	15	3.873 (2.153)
R_{Cmax}	–	NA	15	2.810 (1.514)
λ_{zEFF} (hr^{-1})	–	NA	15	0.0235 (0.0229)
$T_{½EFF}$ (hr)	–	NA	15	55.339 (36.380)

NA=Not applicable
[a] Pre-dose concentration (t=0)
[b] Median (minimum-maximum)
[c] Subjects 001-601 and 001-618 were BLQ, therefore unable to calculate PK parameters
[d] Subject 001-619 did not have concentration data on Day 21; Subject 001-608 excluded due to missed dose on Day 20

Peak exposure (C_{max}) and total exposure (AUC_{0-24}) for imiquimod (R-837) were higher on Day 21 than Day 1 when analysing all patients in the pharmacokinetic population. The mean accumulation ratios, RC_{max} and RAUC, for all patients in the pharmacokinetic population were 2.810 and 3.873, respectively. The serum concentration profile on Day 21 was relatively flat across the dosage interval, and mean C_{max} (0.323±0.159 ng/ml) was less than twice the level of mean C_{min} (0.199±0.109 ng/ml). The mean effective half-life for accumulation was 55.3 hours and the mean observed elimination half-life was 29.3 hours on Day 21. Analysis of trough concentrations over time indicated that steady-state conditions were achieved between Day 7 and Day 14, which was consistent with the time to steady state predicted from the observed elimination half-life (approximately 6 days) and the effective half-life for accumulation (approximately 12 days).

In a comparison of female and male patients who applied imiquimod 3.75% cream to the face, serum pharmacokinetics for imiquimod (R-837) were very similar for both groups on Day 21. In a comparison of scalp and face applications in male patients, imiquimod (R-837) C_{max} and AUC_{0-24} were lower on Day 21 in patients who applied study medication to balding scalp rather than to the face. Analyses of the subgroups were limited by wide variability in the data, small overall numbers, and a large disparity in group sizes (female/male comparison of 4 versus 10 patients, and scalp/face comparison of 3 versus 10 patients).

In conclusion, the amount of imiquimod (R-837) absorbed into systemic circulation after topical application of imiquimod 3.75% cream to the face and/or scalp once daily for up to 21 days was low; peak and total serum imiquimod concentrations increased 3- to 4-fold between Day 1 and Day 21. Steady state was achieved by Day 14. C_{max} and AUC_{0-24} on Day 21 appeared to be similar in female and male patients and lower in male patients who applied imiquimod 3.75% cream to balding scalp rather the face. Imiquimod metabolites (S-26704 and S-27700 combined) were measured, but the data were too sparse to assess.

- Bioavailability

Pharmacokinetic profiles were obtained following single-dose and repeat-dose administration of 3.75% imiquimod cream in Study GW01-0706. The mean (SD) accumulation ratios calculated from C_{max} and

AUC_{0-24} were 2.810 (1.514) and 3.873 (2.153), respectively. The mean effective half-life for accumulation was 55.3 hours and the mean observed elimination half-life was 29.3 hours on Day 21. Analysis of trough concentrations over time indicated that steady-state conditions were achieved between Day 7 and Day 14, which is consistent with the time to steady state predicted from the observed elimination half-life (approximately 6 days) and the effective half-life for accumulation (approximately 12 days).

The following table compares the PK of the already licensed product Aldara® (imiquimod 5% cream) with that of the 3.75% cream.

Table 4: Summary of Systemic Exposure at Steady-State Following Administration of 3.75% or 5% Imiquimod Cream [Mean (SD) Serum Imiquimod C_{max} and AUC_{ss}]

	Cmax (ng/mL)		AUC (ng·hr/mL)	
	Mean (SD)	**Ratio [a]**	**Mean (SD)**	**Ratio [a]**
Study GW01-0706				
2 pkts (18.75 mg) daily to face/scalp	0.323 (0.159)		5.974 (3.088)	
Study 1520-IMIQ [b]				
6 pkts (75 mg) 2 x weekly to > 25% BSA	0.958 (1.18)	2.96	24.3 (26.9)	4.07
Study 1402-IMIQ				
1 pkts (12.5 mg) 3x/week to face	0.120 (0.0629)	0.37	2.06 (1.70)	0.34
2 pkts (25 mg) 3x/week to scalp	0.214 (0.0968)	0.66	4.89 (4.41)	0.82
6 pkts (75 mg) 3x/week to hand/forearms[c]	1.35 (0.841)	4.18	29.1 (17.1)	4.87
6 pkts (75 mg) 3x/week to hand/forearms [d]	3.53 (6.52)	10.92	55.4 (76.0)	9.27

Pkts = packets; BSA= Body surface area

a 5% imiquimod regimen/3.75% imiquimod regimen

b Month 4 data

c Data from Harrison *et al*, 2004[1] (rejecting outliers that were >5X the SD of their respective means)

d Data from the 1402-IMIQ[2] report that includes outliers

2.4.3. Pharmacodynamics

No clinical pharmacodynamic studies were submitted.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetic profiles were obtained following single-dose and repeat-dose administration of 3.75% imiquimod cream in Study GW01-0706. Compared to Aldara 5% cream 2 sachets applied x3/week to scalp, ~20% higher exposure is expected with Zyclara. The relative exposure is approximately 3 times higher when Zyclara is compared to Aldara 1 sachet applied x3/week. According to the European SmPC of Aldara, the most clinically serious adverse event reported following multiple oral doses of 200 mg (content of approximately 21 sachets of Zyclara) was hypotension which resolved following oral or intravenous fluid administration. Therefore, despite relatively higher exposure compared to Aldara, the overall systemic exposure with Zyclara does not seem excessive. These findings, in conjunction with safety findings from submitted clinical trials, including the one year observational study GW01-0803, indicate that the higher systemic exposure with Zyclara does not lead to major safety concerns.

No data on special populations or interactions with other medicines have been provided. The low systemic exposure and the post-marketing data obtained from this and the higher strength of the same active substance (Aldara 5% cream) are reasonably reassuring.

The pharmacodynamic section of the SmPC is based on data obtained from studies on Aldara 5% cream. Given that the same active substance is used in this product, this was considered acceptable.

2.4.5. Conclusions on clinical pharmacology

Data obtained from Study GW01-0706 is considered adequate to further characterise the PK of this product. Bridging to Aldara 5% cream data for the PD section of the SmPC (section 5.1) with regard to the mechanism of action is acceptable.

2.5. Clinical efficacy

2.5.1. Main studies

The data to support this application come from 4 clinical studies with 2 investigational formulations (Imiquimod 2.5% and 3.75% creams), 2 pairs of identically designed studies, with each pair having a different treatment regimen: Studies GW01-0702 and GW01-0704 had 2-week treatment schedules as per the proposed SmPC, whereas GW01-0703 and GW01-0705 had 3-week treatment schedules and are considered as supportive studies accordingly.

GW01-0702 and GW01-0704: **A phase 3, randomised, double-blinded, placebo-controlled, multicentre, efficacy and safety study of four weeks of treatment with imiquimod creams for actinic keratoses**

Methods

Study Participants

Patients had 5 to 20 typical visible or palpable AKs in an area that exceeded 25 cm^2 on either the face or the balding scalp (but not both). Three hundred and nineteen (319) patients with AK were treated.

Actinic keratosis lesions in the defined treatment area (face/balding scalp) were counted by qualified investigators at baseline and at each study visit to determine treatment efficacy. They were diagnosed by clinical inspection as per usual clinical practice. The same evaluator was to count and record the number of AK lesions present in the treatment area throughout the whole study.

Treatments

The scheduling of treatment schedules for the trials are shown below.

Table 5: Visit schedule of the 2-weeks studies GW01-0702 and GW01-0704

Screening	Treatment Cycle 1				Treatment Cycle 2			Follow-up	End of Study
Week -4 to 0	Week 0	Week 1	Week 2		Week 4	Week 5	Week 6	Week 10	Week 14
Visit 1	Visit 2	Visit 3	Visit 4		Visit 5	Visit 6	Visit 7	Visit 8	Visit 9

Note: A no-treatment period of 2 weeks occurred between the 2 treatment cycles.

Study medication was applied in a thin layer once daily to the treatment area (the entire face or the balding scalp, but not both), avoiding the periocular area, lips, and nares. This allowed patients to treat a larger area of sun-damaged skin, including any subclinical lesions that may have been present in the treatment area. As the treatment area was determined to be either the full face or balding scalp,

patients did not need to remember the outline of a fixed (25 cm^2) patch of skin designated for treatment.

A maximum of 2 sachets of study medication, total 500 mg cream including 18.75 mg imiquimod, was applied daily for 2 week treatment cycles separated by a 2-week no-treatment cycle.

In addition, all patients who showed complete clearance at the end of one of the 2 pivotal studies were invited to be monitored for one year.

Objectives

The studies were designed to compare the efficacy of the individual imiquimod cream formulations 3.75% and 2.5% to vehicle.

Outcomes/endpoints

For all studies the primary endpoint was the proportion of patients for whom the AKs were completely cleared. For Studies 0702 and 0704 this was at 14 weeks. Secondary endpoints were partial clearance rates (75% reduction in AKs) and the percent change in total number of lesions from baseline.

Randomisation

Eligible patients were centrally randomised to placebo, imiquimod 2.5%, or imiquimod 3.75% (1:1:1).

Statistical methods

For the purposes of the comparison of imiquimod to placebo the hypothesis testing was planned and performed using a hierarchical procedure (modified Bonferroni-Holm procedure).

Missing data were handled using Last observation Carried Forward (LOCF). Additional analysis of the primary efficacy variable was performed in which all missing observations were considered “not cleared” (i.e. counted as failures). The Cochran-Mantel-Haenzel test, adjusting for site, was used to analyse the data. To control for the 2 doses, Hochberg’s modification of the Bonferroni procedure was used. After this, the 2 doses were tested against each other at the 5% level.

Results

Baseline data

The patient disposition tables for all 4 studies are shown below:

Table 6: Patient disposition in study 0702

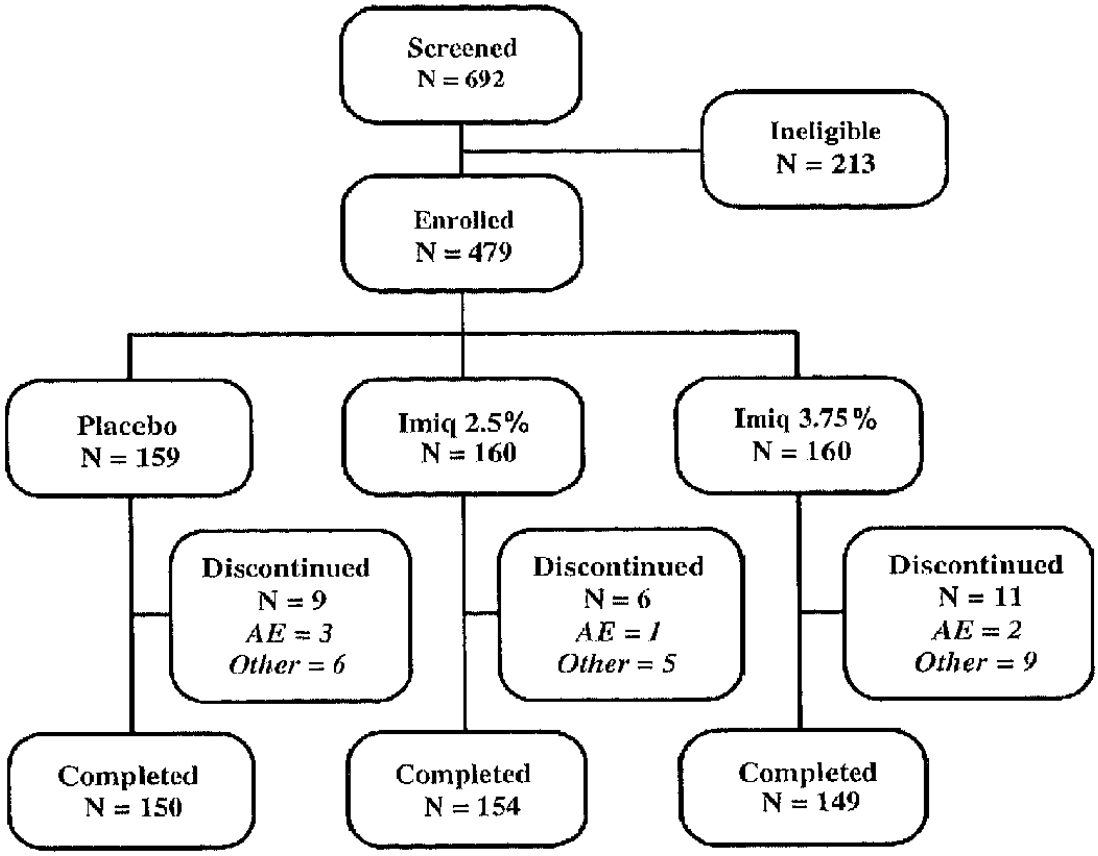
	Imiquimod Cream			
	2.5%	3.75%	Placebo	Overall
Total no. of subjects, n (%)				
Screened				364
Randomized	81	81	80	242
Completed study	78 (96.3)	74 (91.4)	75 (93.8)	227 (93.8)
Discontinued study	3 (3.7)	7 (8.6)	5 (6.3)	15 (6.2)
Reasons for discontinuation from the study, n (%[a])				
Safety reasons (AEs)	1 (1.2)	1 (1.2)	2 (2.5)	4 (1.7%)
Investigator's request	0	0	0	0
Subject's request (not AE)	1 (1.2)	3 (3.7)	2 (2.5)	6 (2.5)
Noncompliance	0	0	0	0
Use of concomitant therapy	0	1 (1.2)	0	1 (0.4)
Lost to follow-up	1 (1.2)	2 (2.5)	1 (1.3)	4 (1.7)
Other (not AE)	0	0	0	0

Table 7: Patient disposition in study 0704

	Imiquimod Cream			
	2.5%	3.75%	Placebo	Overall
Total no. of subjects, n (%)				
Screened				328
Randomized	79	79	79	237
Completed study	76 (96.2)	75 (94.9)	75 (94.9)	226 (95.4)
Discontinued study	3 (3.8)	4 (5.1)	4 (5.1)	11 (4.6)
Reasons for discontinuation from the study, n (%[a])				
Safety reasons (AEs)	0	1 (1.3)	1 (1.3)	2 (0.8)
Investigator's request	0	0	0	0
Subject's request (not AE)	1 (1.3)	1 (1.3)	2 (2.5)	4 (1.7)
Noncompliance	0	1 (1.3)	0	1 (0.4)
Use of concomitant therapy	0	0	1 (1.3)	1 (0.4)
Lost to follow-up	1 (1.3)	0	0 (0.0)	1 (0.4)
Other (not AE)	1 (1.3)	1 (1.3)	0	2 (0.8)

Participant flow

Participant flow for the GW01-0702 and GW01-0704 studies



Outcomes and estimation

The tables below summarise the primary efficacy data of the 2 studies submitted.

Table 8: Percentage of patients with complete clearance at end of pivotal study 0702

	Imiquimod Cream		
	2.5%	3.75%	Placebo
ITT Population (all subjects with missing data were counted as failures), N	81	81	80
n/N (%)	19/81 (23.5)	21/81 (25.9)	2/80 (2.5)
95% CI	14.8, 34.2	16.8, 36.9	0.3, 8.7
P value vs Placebo[a]	<.001**	<.001**	NA
P value vs 3.75% Imiquimod Cream[a]	0.777	NA	NA

Table 9: Percentage of patients with complete clearance at end of pivotal study 0704

	Imiquimod Cream		
	2.5%	3.75%	Placebo
ITT Population (all subjects with missing data were counted as failures), N	79	79	79
n/N (%)	29/79 (36.7)	36/79 (45.6)	8/79 (10.1)
95% CI	26.1, 48.3	34.3, 57.2	4.5, 19.0
P value vs Placebo[a]	<0.001**	<0.001**	NA
P value vs 3.75% Imiquimod Cream[a]	0.275	NA	NA

95% CI = 95% Confidence interval, N = Number of subjects in the analysis; NA = Not applicable, vs = Versus, n/N = Number of subjects with complete clearance at end of study divided by the number of subjects analyzed.

a: *P* values are from Cochran-Mantel-Haenszel test, stratified by analysis site, taking 2 treatment groups at a time. *P* values marked with ** are statistically significant using Hochberg's modified Bonferroni procedure.

For the combined trials the complete clearance rate of the full face or balding scalp under Zyclara 3.75% cream was 35.6 % (57/160 patients, CI 28.2%, 43.6 %) under vehicle 6.3% (10/159 patients, CI 3.1%, 11.3%) at the 8-week post-treatment visit.

Supportive studies

GW01-0703 and GW01-0705: A phase 3, randomized, double-blinded, placebo-controlled, multicenter, efficacy and safety study of six weeks of treatment with imiquimod creams for actinic keratoses

These 2 studies have the same design as the pivotal studies, the only difference being the treatment regimen of 3-week cycle instead of 2-week cycle.

End of study (EOS, 8 weeks post end of treatment, Week 17 based on study design) was the time point used for evaluation of the primary (complete clearance) and two secondary (partial clearance, percent AK lesion reduction) efficacy endpoints.

Table 10: Visit schedule of the 3-weeks studies GW01-0703 and GW01-0705

Table 9–1 Study Design

Screening	Treatment Cycle 1					Treatment Cycle 2				Follow-up	End of Study
Week -4 to 0	Week 0	Week 1	Week 2	Week 3		Week 6	Week 7	Week 8	Week 9	Week 13	Week 17
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11

Note: A no-treatment period of 3 weeks occurred between treatment cycles.

The baseline data are shown below.

Table 11: Patient disposition in study 0703

	Imiquimod Cream			
	2.5%	3.75%	Placebo	Overall
Total no. of subjects, n (%)				
Screened	--	--	--	340
Randomized	82	80	78	240
Completed study	77 (93.9)	76 (95.0)	73 (93.6)	226 (94.2)
Discontinued study	5 (6.1)	4 (5.0)	5 (6.4)	14 (5.8)
Reasons for discontinuation from the study, n (%[a])				
Safety reasons (AEs)	1 (1.2)	2 (2.5)	0 (0.0)	3 (1.3)
Investigator's request	0	0	0	0
Subject's request (not AE)	3 (3.7)	2 (2.5)	4 (5.1)	9 (3.8)
Noncompliance	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.4)
Use of concomitant therapy	0	0	0	0
Lost to follow-up	0	0	0	0
Other (not AE)	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)

Table 12: Patient disposition in study 0705

	Imiquimod Cream			
	2.5%	3.75%	Placebo	Overall
Total no. of subjects, n (%)				
Screened				326
Randomized	82	82	86	250
Completed study	80 (97.6)	76 (92.7)	81 (94.2)	237 (94.8)
Discontinued study	2 (2.4)	6 (7.3)	5 (5.8)	13 (5.2)
Reasons for discontinuation from the study, n (%[a])				
Safety reasons (AEs)	1 (1.2)	2 (2.4)	1 (1.2)	4 (1.6)
Investigator's request	0	0	0	0
Subject's request (not AE)	0	2 (2.4)	0	2 (0.8)
Noncompliance	0	0	0	0
Use of concomitant therapy	0	0	0	0
Lost to follow-up	0 (0.0)	1 (1.2)	1 (1.2)	2 (0.8)
Other (not AE)	1 (1.2)	1 (1.2)	3 (3.5)	5 (2.0)

AE = Adverse event.
a: Percentage of randomized population.

The tables below summarise the primary efficacy data

Table 13: Percentage of patients with complete clearance at end of study 0703

	Imiquimod Cream		
	2.5%	3.75%	Placebo
ITT Population (all subjects with missing data were counted as failures), N	82	80	78
n/N (%)	19/82 (23.2)	26/80 (32.5)	3/78 (3.8)
95% CI	14.6, 33.8	22.4, 43.9	0.8, 10.8
P value vs Placebo[a]	<0.001**	<0.001**	--
P value vs 3.75% Imiquimod Cream[a]	0.170	--	--

Table 14: Percentage of patients with complete clearance at end of study 0705

	Imiquimod Cream		
	2.5%	3.75%	Placebo
ITT Population (all subjects with missing data were counted as failures), N	82	82	86
n/N (%)	21/82 (25.6)	29/82 (35.4)	4/86 (4.7)
95% CI	16.6, 36.4	25.1, 46.7	1.3, 11.5
P value vs Placebo[a]	<0.001**	<0.001**	NA
P value vs 3.75% Imiquimod Cream[a]	0.194	NA	NA

95% CI = 95% Confidence interval, N = Number of subjects in the analysis; NA = Not applicable, vs = Versus, n/N = Number of subjects with complete clearance at end of study divided by the number of subjects analyzed.
a: *P* values are from Cochran-Mantel-Haenszel test, stratified by analysis site, taking 2 treatment groups at a time. *P* values marked with ** are statistically significant using Hochberg's modified Bonferroni procedure.

Study GW01-0803 was a follow-up observational study to evaluate sustained clearance rates of actinic keratoses up to one year after completion of studies GW01-0702, GW01-0703, GW01-0704, and GW01-0705. At the 12 month follow-up timepoint, the sustained clearance rate was 40.5% in patients previously treated with the 3.75% 2-week treatment cycle regimen. Overall, slightly higher rates of sustained complete clearance were observed in patients previously treated with imiquimod 3.75% versus 2.5% and with 3-week versus 2-week treatment cycle regimens.

Table 15: Sustained complete clearance rate of actinic keratosis lesions in the previous treatment area (2-week treatment cycle regimen, all evaluable patients)

	Imiquimod Cream		
	3.75% (N = 42)	2.5% (N = 39)	Placebo (N = 8)
12-month follow-up visit			
Missing	2/42 (4.8)	0	0
Subjects who remained clear of AK lesions, n (%)[a]	17/42 (40.5)	13/39 (33.3)	5/8 (62.5)
95% Confidence interval	25.6, 56.7	19.1, 50.2	24.5, 91.5
Subjects with recurrence of AK lesions n (%)[b]	23/42 (54.8)	26/39 (66.7)	3/8 (37.5)
95% Confidence interval	38.7, 70.2	49.8, 80.9	8.5, 75.5

a: Includes those subjects who had a visit with no AK lesions.
b: Recurrence was carried forward.

Table 16: Sustained complete clearance rate of actinic keratosis lesions in the previous treatment area (3-week treatment cycle regimen, all evaluable patients)

	Imiquimod Cream		
	3.75% (N = 48)	2.5% (N = 37)	Placebo (N =3)
12-month follow-up visit			
Missing	5/48 (10.4)	2/37 (5.4)	0
Subjects who remained clear of AK lesions, n (%)[a]	23/48 (47.9)	16/37 (43.2)	3/5 (60.0)
95% Confidence interval	33.3, 62.8	27.1, 60.5	14.7, 94.7
Subjects with recurrence of AK lesions n (%)[b]	20/48 (41.7)	19/37 (51.4)	2/5 (40.0)
95% Confidence interval	27.6, 56.8	34.4, 68.1	5.3, 85.3

a: Includes those subjects who had a visit with no AK lesions
b: Recurrence was carried forward.

Study GW01-0901 was a multicenter, randomised, double-blind, placebo-controlled study, in which the efficacy and safety of imiquimod 3.75% cream following cryosurgery to treat clinically typical visible or palpable AK lesions on the face was compared with that of placebo cream. The cryosurgery/imiquimod 3.75% group achieved significantly greater efficacy than the cryosurgery/placebo group in terms of percent reduction of all AK lesions, cryosurgery-treated AK lesions, and non-cryosurgery-treated AK lesions from baseline to Week 26/end of study (EOS) in the ITT population. The primary endpoint, percent reduction from baseline to Week 26/EOS of all AK lesions, showed a median percent reduction of 86.5% with imiquimod 3.75% treatment compared with a 50.0% reduction with placebo treatment.

2.5.2. Discussion on clinical efficacy

Design and conduct of the clinical studies submitted were considered appropriate for this hybrid application. The choice of primary and secondary endpoints and the inclusion/exclusion criteria were also considered acceptable.

The statistical methods used to analyse the data are acceptable. The use of LOCF may not be appropriate and the use of missing = failure may be more appropriate. The Applicant has presented both analyses which was considered sufficient. The procedure to control the Type I error was acceptable.

The Applicant has adequately described the patient population. There were very little missing data and thus the sensitivity analyses should provide similar results to the main analyses. There did not appear to be a difference between the doses, or the reasons for withdrawal, either within or between studies.

The Applicant has provided clear statistical evidence of efficacy over placebo for both doses. The pre-specified primary analysis using LOCF (not shown) showed similar results. Although none of the studies showed a formal separation of the doses, the studies were never powered to do this and 3 of the 4 studies show a clear numerical separating.

It is also noted that in general there does not seem to be a substantial benefit using 3-week treatment as opposed to 2-week treatment. Whilst this should be treated with caution as cross-trial comparisons are non-randomised comparisons, the evidence generated to date does suggest there is little benefit from the longer treatment regimen and thus the one proposed by the applicant is acceptable.

All secondary endpoints (not shown) showed very similar results, with highly significant effects over placebo and no statistical difference between doses, albeit with a numerical difference.

No overall differences in safety or effectiveness were observed between patients 65 years or older and the younger patients.

2.5.3. Conclusions on the clinical efficacy

Superior efficacy of Zyclara 3.75% cream in comparison to placebo in the treatment of AK has been demonstrated. Given that Zyclara is not intended for interchangeable use with Aldara, formal therapeutic equivalence data are not deemed necessary. However, lack of active comparator data to a first line treatment, limits the use of Zyclara to second line therapy as is the case with the reference product, Aldara.

2.6. Clinical safety

Patient exposure

The safety database on Imiquimod 3.75% cream includes 969 patients. Approximately 85% showed a transitory increase in AK lesions count during one course of treatment. The lesions decreased during the treatment interval and the treatment free follow-up periods. The patient population enrolled in the study were predominantly male, Caucasian, elderly, with multiple AKs over a wide area of sun-exposed facial or scalp skin and thus reflecting the target population of AK patients.

The study program excluded pregnant and lactating women, patients with renal, hepatic or cardiac impairments, patients with polymorphism, and children (there were no participants under the age of 33). In addition, patients who were treated with immune-modulators or immunosuppressive therapy were excluded (only inhaled/ intranasal steroids were permitted).

Adverse events

The drug exposure for Imiquimod 3.75% cream using the recommended regimen of daily treatment for 2x2 weeks was higher (18.75 mg/ day) than the exposure for the currently licensed Imiquimod 5% cream (12.5 mg/ treatment day). No new safety signals were identified during the pivotal clinical trial program. Most patients experienced local skin reactions, which subsided with completion of each treatment cycle. Some patients discontinued as a result of adverse events.

Table 17: Exposure in the 2 pivotal studies (GW01-0702 and GW01-0704) and studies GW01-0703 and GW01-0705

	2-week regimen	3-week regimen

	3.75%	2.5%	VEH	3.75%	2.5%	VEH
Duration of treatment [days]						
N Mean (SD) Median	160 26.3 (4.5) 28	160 27.6 (2.0) 28	159 26.9 (3.8) 28	161 38.4 (7.4) 42	164 39.5 (6.9) 42	163 41.1 (3.8) 42
Total amount of drug used [mg]						
Mean (SD) Median Theoret.Max.	400 (125) 436 525	291 (79) 325 350	- - -	571 (180) 591 788	410 (126) 459 525	- - -
Rest periods taken by patients						
N	17	11	0	44	28	0
%	10.6	6.9	0	27.2	17.1	0

11% of patients receiving imiquimod 3.75% cream in the proposed 2-week regimen during the pivotal studies required periods of treatment interruption due to adverse events.

A range of adverse reactions concerning the reproductive system and breast disorders are included in the EU SmPC for Aldara. Imiquimod 3.75% cream is not indicated for perianal and genital warts. However, due to a potential of off-label use, adverse reactions of the reproductive system and breast disorders should be included in the SmPC for imiquimod 3.75% cream.

As expected, higher rates of AEs were observed with active treatment compared to vehicle with a dose and duration dependent pattern (higher rate of AEs in 3.75% vs 2.5% cream and in 3 week vs 2 week duration of treatment). The AEs reported were generally consistent with those previously identified with Aldara 5%.

Serious adverse event/deaths/other significant events

Table 18: All Serious Adverse Events in 2-Week Treatment Cycle Studies

Treatment Regimen	Site/Subject No.	Adverse Event	Severity	Relation to Treatment	Onset Day/ Resolution Day	Action Taken/Outcome
3.75% (2-week)	**04/205**	**Cerebrovascular accident**	Severe	Not related	45 / 48	Medication prescribed, other treatment; resolved
		Atrial fibrillation	Severe	Not related	45 / 48	Medication prescribed, other treatment; resolved
	04/211	**Small intestine obstruction**	Moderate	Not related	3 / 7	Study product interrupted, medication prescribed, other treatment; resolved
		Small intestine obstruction	Moderate	Not related	91 / 99	Medication prescribed; resolved
	27/425	**Anxiety**	Severe	Not related	49 / 50	Other treatment; resolved
	33/410	**Chest pain**	Moderate	Not related	60 / 62	Medication prescribed, other treatment; resolved
	36/415	**Diarrhea**	Severe	Probably related	11 / 22	Study product discontinued, medication prescribed; resolved
2.5% (2-week)	08/213	Pneumonia bacterial	Severe	Not related	47 / 67	Medication prescribed; resolved
		Acute myocardial infarction	Moderate	Not related	48 / 49	Medication prescribed; resolved
	11/205	Non-cardiac chest pain	Mild	Not related	14 / 16	Medication prescribed; resolved
	12/221	Pneumonia	Severe	Not related	25 / 34	Medication prescribed resolved
	31/420	Angina pectoris	Severe	Not related	88 / 90	Medication prescribed, other treatment; resolved
	34/404	Atrial fibrillation	Severe	Not related	41 / 44	Other treatment; resolved
Placebo (2-week)	03/227	Intestinal obstruction	Severe	Not related	74 / 80	Medication prescribed, other treatment; resolved
	04/206	Prostatitis	Moderate	Not related	72 / 74	Medication prescribed; resolved

Note: Data for the proposed regimen (3.75% imiquimod 2-week treatment cycle) are bolded.

The incidence of SAEs was low and they were mostly unrelated to Zyclara.

The following table presents data reflecting the exposure to Zyclara or vehicle in the pivotal studies (frequencies very common to uncommon and at greater frequency after vehicle) and the experience with imiquimod 5% cream.

System organ class	Frequency	Adverse reactions
Infections and infestations	Common	Herpes simplex
	Uncommon	Infection
		Pustules
	Frequency not known	Skin infection (While serious sequelae have not resulted, the possibility of infection in broken skin should always be considered)
Blood and lymphatic system disorders	Common	Lymphadenopathy
	Frequency not known	Haemoglobin decreased
		White blood cell count decreased
		Neutrophil count decreased
		Platelet count decreased
Immune system disorders	Rare	Exacerbation of autoimmune conditions
Metabolism and nutrition disorders	Common	Anorexia
		Blood glucose increased
Psychiatric disorders	Common	Insomnia
	Uncommon	Depression
		Irritability
Nervous system disorders	Common	Headache
		Dizziness
Eye disorders	Uncommon	Conjunctival irritation
		Eyelid oedema
Respiratory, thoracic and mediastinal disorders	Uncommon	Nasal congestion
		Pharyngo laryngeal pain
Hepatobiliary disorders	Frequency not known	Hepatic enzyme increased
Gastrointestinal disorders	Common	Nausea
		Diarrhoea
		Vomiting
	Uncommon	Dry mouth
Skin and subcutaneous tissue disorders	Very common	Erythema
		Scab
		Skin exfoliation
		Skin oedema
		Skin ulcer
		Skin hypopigmentation
	Common	Dermatitis
	Uncommon	Face oedema
	Rare	Remote site dermatologic reaction (Rare cases of remote site dermatologic reactions, including erythema multiforme, have been reported from clinical trials with imiquimod 5% cream therapy)
	Frequency not known	Alopecia (Clinical studies investigating the use of imiquimod 5% cream for the treatment of actinic keratosis have detected a 0.4% (5/1214) frequency of alopecia at the treatment site or surrounding area.)
		Erythema multiforme
		Stevens Johnson syndrome
		Cutaneous lupus erythematosus
		Skin hyperpigmentation
Musculoskeletal and connective tissue disorders	Common	Myalgia
		Arthralgia
	Uncommon	Back pain
		Pain in extremity
General disorders and administration site conditions	Very common	Application site erythema
		Application site scabbing
		Application site exfoliation

		Application site dryness
		Application site oedema
		Application site ulcer
		Application site discharge
	Common	Application site reaction
		Application site pruritus
		Application site pain
		Application site swelling
		Application site burning
		Application site irritation
		Application site rash
		Fatigue
		Pyrexia
		Influenza-like illness
		Pain
		Chest pain
	Uncommon	Application site dermatitis
		Application site bleeding
		Application site papules
		Application site paraesthesia
		Application site hyperaesthesia
		Application site inflammation
		Application site scar
		Application site skin breakdown
		Application site vesicles
		Application site warmth
		Asthenia
		Chills
		Lethargy
		Discomfort
		Inflammation

The long-term safety of imiquimod was assessed in study GW01-0803 which was a one year observational follow-up to Studies GW01-0702, GW01-0703, GW01-0704, and GW01-0705. The safety results of this study are summarised below.

Table 19: Summary of the GW01-0803 safety results

	Imiquimod Cream		
	3.75% (N=90)	2.5% (N=76)	Placebo (N=13)
Subjects with any AE, n (%)	7 (7.8)	5 (6.6)	0 (0.0)
Number of AEs	7	6	0
Subjects with any:			
Previous Phase 3 treatment-related AE, n (%)[a]	1 (1.1)	0 (0.0)	0 (0.0)
SAE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
AEs of severe intensity, n (%)	0 (0.0)	0 0.0)	0 (0.0)
AE leading to study discontinuation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects by Preferred Term			
Basal cell carcinoma	3 (3.3)	0	0
Squamous cell carcinoma	1 (1.1)	1 (1.3)	0
Application site dermatitis	1 (1.1)	0	0
Application site pruritus	0	1 (1.3)	0
Application site scar	1 (1.1)	0	0
Folliculitis	0	1 (1.3)	0
Oral herpes	0	1 (1.3)	0
Rosacea	1 (1.1)	0	0
Seborrhoeic dermatitis	0	1 (1.3)	0
Seborrhoeic keratosis	0	1 (1.3)	0

Laboratory findings

Clinical laboratory analysis results were similar in both the 2-week and 3-week treatment cycle studies. Examination of the shift tables for laboratory data revealed no trends. For most of the haematology, chemistry, and urinalysis variables, the majority of patients were normal at screening and at the end of the study. Occasional shifts from within the normal range to above or below the limits of the normal range were observed in all 3 treatment groups for most laboratory tests in both the pivotal and supportive studies.

Safety in special populations

Adverse events were examined in the pivotal and supportive studies by demographic subpopulations. The incidence of AEs tended to be somewhat higher in patients with Fitzpatrick skin type I or II than in those with type III-VI, and in patients who treated the face than in those who treated the balding scalp in the active treatment groups, but there were no other apparent trends within the subgroups. Of note, approximately half of the study populations was 65 years or older.

Safety related to drug-drug interactions and other interactions

No interaction studies have been performed. This includes studies with immunosuppressive drugs. Interactions with systemic drugs would be limited by the minimal percutaneous absorption of imiquimod cream. Due to its immunostimulating properties, imiquimod cream should be used with caution in patients who are receiving immunosuppressive medicinal products.

The concomitant use of Zyclara and any other imiquimod creams in the same treatment area should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of local skin reactions.

Discontinuation due to adverse events

In the pivotal studies, 6 patients reported 9 AEs that led to discontinuation from the study: 2 patients in the 3.75% imiquimod group, 1 patient in the 2.5% imiquimod group, and 3 patients in the placebo group. Five of these events were considered to be related or probably related to study treatment by the investigator. None of the AEs leading to withdrawal from the 2-week treatment cycle studies were categorized as SAEs.

Post marketing experience

Cumulative post-marketing experience since 1997 was available for Imiquimod 5%. The MEDA safety database for imiquimod in all indications contained a total of 3282 individual medically confirmed case reports. Of these, 407 cases were serious and unlisted.

As of 27 April 2010, a PSUR covering information from both, Aldara 5% and Zyclara (Imiquimod 3.75% cream) was issued. According to this PSUR, no new relevant safety findings have been identified from postmarketing adverse events reports coincident with the appearance of imiquimod 3.75% cream on the market in the US and Canada. These safety data are in accordance with the safety information presented in the proposed SmPC.

2.6.1. Discussion on clinical safety

Clinical safety of the reference product (Aldara 5% cream) in the treatment of actinic keratosis is well-established.

With respect to tolerability and safety of the 2-week versus 3-week treatment regimens, similar dose-response relationship was seen with respect to local skin reactions and certain systemic reactions that are considered to be attributable to local cytokine release triggered by imiquimod. In contrast to the efficacy estimates, the incidence of adverse reactions appeared to be higher in the 3-week regimen than in the 2-week regimen. For instance, the number of rest periods taken, mainly triggered by local skin and applications site reactions, increased strongly from the 2-week (10.6% of patients) to the 3-week regimen (27.2% of patients).

Therefore, the Applicant primarily proposed for the 3.75% strength to be applied daily (up to two sachets) for 2 treatment cycles of 2 weeks each, separated by a 2-week treatment pause.

Zyclara at the proposed posology leads to a higher systemic exposure compared to Aldara when used for the treatment of AK. This higher exposure did not lead to any new safety signals during the pivotal clinical trials with Zyclara. It is also noted that the clinical development program of Zyclara did not include a formal head to head comparison with Aldara. However, the applicant following CHMP request, provided this comparison.

With respect to local skin reactions, the following comparison of Zyclara versus Aldara data is provided in Table 20. It shows that the incidence of severe local skin reactions is not consistently different when using Zyclara 3.75% in the 2-week regimen compared to using Aldara 5% in the 1-2 COT regimen. Such outcome is to be expected given the known qualitatively comparable efficacy. Note that many of these skin reactions were already present at baseline as signs of severity of the target disease AK, although often only of mild and never of severe severity. Therefore, the threshold “severe” is most sensitive for such a comparison.

Table 20: Comparison of severe local skin reactions in the treatment area

	Zyclara 2-week studies (GW01-0702+0704)		Aldara COT-studies (1473-IMIQ+1487-IMIQ)	
	Zyclara (N=160)	Vehicle (N=159)	Aldara (N=251)	Vehicle (N=252)
Erythema	40 (25.2)	0 (0.0)	62 (24.7)	2 (0.8)
Scabbing/Crusting	22 (13.8)	0 (0.0)	48 (19.1)	5 (2.0)
Flaking/Scaling/Dryness	13 (8.2)	2 (1.3)	32 (12.7)	9 (3.6)
Oedema	9 (5.7)	0 (0.0)	18 (7.2)	1 (0.4)
Erosion/Ulceration	17 (10.7)	0 (0.0)	17 (6.8)	1 (0.4)
Weeping/Exudate	9 (5.7)	0 (0.0)	n.av.	n.av.

Shown are patients with worst severity = severe at any time during the studies.
Sources: Zyclara: Integrated summary of safety, table 5.3.5.3.2-15;
Aldara: Integrated summary of safety, table 5.3.5.3.2-15

During therapy and until healed, affected skin is likely to appear noticeably different from normal skin. Local skin reactions are common but these reactions generally decrease in intensity during therapy or resolve after cessation of imiquimod cream therapy. Rarely, intense local inflammatory reactions including skin weeping or erosion can occur after only a few applications of imiquimod cream.

There is an association between the complete clearance rate and the intensity of local skin reactions (e.g. erythema). These local skin reactions may be related to the stimulation of local immune response. Furthermore, imiquimod has the potential to exacerbate inflammatory conditions of the skin. If required by the patient's discomfort or the intensity of the local skin reaction, a rest period of several days may be taken. Treatment with imiquimod cream can be resumed after the skin reaction has moderated. The intensity of the local skin reactions tend to be lower in the second cycle than in the first treatment cycle with Zyclara.

The other important expected part of side effects are systemic reactions attributable to a spillover of local cytokine release into systemic circulation, summarised in the following tables.

Table 21: Comparison of potential systemic events

	Aldara AK-COT 1473- and 1487-IMIQ		New Imiquimod 3.75% project 4 pivotal GW studies combined			GW01-0901	
	5%	VEH	3.75%	2.5%	VEH	3.75%	VEH
Safety set (100%)	252	254	322	324	323	126	121
Headache	9 (3.6)	3 (1.2)	18 (5.6)	9 (2.8)	6 (1.9)	3 (2.4)	0
Fatigue	5 (2.0)	0	15 (4.7)	7 (2.2)	1 (0.3)	5 (4.0)	1 (0.8)
Myalgia	5 (2.0)	0	6 (1.9)	1 (0.3)	0	6 (4.8)	1 (0.8)
Lymphadenopathy	2 (0.8)	0	10 (3.1)	8 (2.5)	0	2 (1.6)	0
Fever / pyrexia*	3 (1.2)	0	11 (3.4)	1 (0.3)	0	3 (2.4)**	1 (0.8)**
Nausea	3 (1.2)	2 (0.8)	8 (2.5)	3 (0.9)	2 (0.6)	6 (4.8)	0
URTI	29 (7.5)	44 (11.3)	8 (2.5)	8 (2.5)	7 (2.2)	7 (5.6)	9 (7.4)

This table is confined to preferred terms (disregarding causality assessments!) with trend-like ($p < 0.1$) difference to vehicle in either the Imiquimod 5%-AK project or the new Imiquimod 3.75% -AK project, in addition nausea, as it was notable in study GW01-0901.

* In the Aldara project only "fever" was coded, while in the Imiquimod 3.75% project only "pyrexia" was coded.

** Such terms were coded as "influenza-like illness" in study GW01-0901.

Table 22: Comparison of potential systemic events, confined to 2-week regimen

	Aldara AK-COT 1473- and 1487-IMIQ		New Imiquimod 3.75% project GW01-0702 and GW01-0704			GW01-0901	
	5%	VEH	3.75%	2.5%	VEH	3.75%	VEH
Safety set (100%)	252	254	160	160	159	126	121
Headache	9 (3.6)	3 (1.2)	10 (6.3)	3 (1.9)	5 (3.1)	3 (2.4)	0
Fatigue	5 (2.0)	0	7 (4.4)	2 (1.3)	0	5 (4.0)	1 (0.8)
Myalgia	5 (2.0)	0	1(0.6)	1(0.6)	0	6 (4.8)	1 (0.8)
Lymphadenopathy	2 (0.8)	0	3 (1.9)	4 (2.5)	0	2 (1.6)	0
Fever / pyrexia*	3 (1.2)	0	5(3.1)	0	0	3 (2.4)**	1 (0.8)**
Nausea	3 (1.2)	2 (0.8)	6 (3.8)	1 (0.6)	2 (1.3)	6 (4.8)	0
URTI	29 (7.5)	44 (11.3)	4 (2.5)	0	4 (2.5)	7 (5.6)	9 (7.4)

This table is confined to the preferred terms presented in Table 9 (above).

* In the Aldara project only "fever" was coded, while in the imiquimod 3.75% project only "pyrexia" was coded.

** Such terms were coded as "influenza-like illness" in study GW01-0901.

Flu-like systemic signs and symptoms may accompany, or even precede, intense local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, and chills. An interruption of dosing or dose adjustment should be considered. Imiquimod should be used with caution in patients with reduced haematologic reserve.

The safety and efficacy of Zyclara in immunocompromised patients (e.g. organ transplant patients) and/or patients with autoimmune conditions have not been established. Therefore, imiquimod cream should be used with caution in these patients (see section 4.5). Consideration should be given to balancing the benefit of imiquimod treatment for these patients with the risk associated either with the possibility of organ rejection or graft-versus-host disease or a possible worsening of their autoimmune condition.

No data are available on re-treating actinic keratoses that have cleared after two cycles of treatment and subsequently recur.

For imiquimod no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Zyclara should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

The long-term safety aspect was assessed in study GW01-0803. During this follow-up study, basal cell carcinoma and squamous cell carcinoma were the most frequently reported AEs in the study. Squamous cell or basal cell carcinoma was reported in 4 patients in the 3.75% imiquimod, 3-week treatment cycle regimen and basal cell carcinoma was reported in 1 patient in the 2.5% imiquimod, 2-week treatment cycle regimen. 3 out of 4 of these patients had a reported history of basal cell or squamous cell carcinoma. On all 4 occasions, the investigators' assessment of causality was 'not related' (in 1 case 'probably not related') to study medication.

These results were not alarming and could hardly be linked to slightly higher systemic exposure seen with Zyclara. However, the applicant was requested to include the two studies X-03016-3271 and X-03016-3284, implemented as part of the Aldara (imiquimod 5%) RMP, in the RMP of Zyclara to gather long-term data on recurrences of actinic keratosis and progression to superficial squamous cell carcinoma.

2.6.2. Conclusions on the clinical safety

Safety of Zyclara in the treatment of AK at the proposed posology and for the duration of pivotal clinical trials has been demonstrated. A comparison between AE and SAE data of Zyclara vs Aldara indicate local skin reactions for both treatments are comparable and reactions are mostly reflective of the therapeutic action of imiquimod. Comparative data for 2-week regimen – in line with the proposed duration of treatment – shows that the rates of systemic AEs are generally low for both treatments, and numerically slightly in favour of Zyclara (with the exception of lymphadenopathy which was seen in 1.9% of patients who received the 3.75% cream compared to 0.8% of those who received Aldara). It can be concluded that the safety profile of Zyclara is comparable to that of Aldara.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Risk management plan

The applicant submitted a risk management plan

Table 22: Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks		
▪ **Stimulation or exacerbation of (auto) immune conditions**	• Routine pharmacovigilance	SmPC will state: ***4.4 Special warnings and special precautions for use*** *The safety and efficacy of Zyclara in immunocompromised patients (e.g. organ transplant patients) and/or patients with autoimmune conditions have not been established.* *Therefore, imiquimod cream should be used with caution in these patients (see section 4.5). Consideration should be given to balancing the benefit of imiquimod treatment for these patients with the risk associated either with the possibility of organ rejection or graft-versus-host disease or a possible worsening of their autoimmune condition.* ***4.8 Undesirable effects*** *Rare: Exacerbation of autoimmune conditions*
▪ **Serious skin reactions**	• Routine pharmacovigilance	SmPC will state: ***4.8 Undesirable effects*** *Rare: Remote site dermatologic reaction (Rare cases of remote site dermatologic reactions, including erythema multiforme, have been reported from clinical trials with imiquimod 5% cream therapy)* *Frequency not known: Erythema multiforme, Stevens Johnson syndrome, Cutaneous lupus erythematosus*

Important potential risks		
▪ **Risk of progression to invasive SCC**	• Routine pharmacovigilance • Continuation of collection of information on recurrence of AK and progression to SCC in Aldara Studies X-03016-3271 and X-03016-3284	SmPC will state: ***5.1 Pharmacodynamic properties*** *Squamous cell carcinoma (SCC) was reported in 1.3% (2/160) of patients treated with Zyclara, in 0.6% (1/159) treated with vehicle. This difference was not statistically significant.*
▪ **Viral infections**	• Routine pharmacovigilance	SmPC will state: ***4.8 Undesirable effects*** *Common: Herpes simplex* *Uncommon: Infection*
▪ **Angiooedema / capillary leak syndrome (Hypersensitivity)**	• Routine pharmacovigilance	SmPC will state: ***4.3 Contraindications*** *Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.*
▪ **Cardiovascular disease and related symptoms**	• Routine pharmacovigilance • Study GW01-1001	*.SmPC will state:* ***4.4 Special warnings and special precautions for use*** ***Special population*** *Patients with cardiac, hepatic or renal impairment were not included in clinical trials.Caution should be exercised in these patients.*
▪ **Hepatobiliary disorders**	• Routine pharmacovigilance	SmPC will state: ***4.8 Undesirable effects*** *Frequency not known: Hepatic enzyme increased*
▪ **Off-label use in perianal and genital warts** (for which Imiquimod 5% is registered in the EU)	• Routine pharmacovigilance	
Important missing information		
Long-term data on recurrence of AK and progression to SCC following treatment with Aldara with a 3 year follow-up period	▪ Routine Pharmacovigilance ▪ Aldara Studies X-03016-3271 and X-03016-3284, cf. Annex 5	Adequate information provided in the SmPC (Routine) ***4.4 Special warnings and special precautions for use*** Re-treatment *No data are available on re-treating actinic keratosis that have cleared after two cycles of treatmentand subsequently recur.*

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
To submit the final study report for study X-03016-3271 investigating the long term effect of Aldara in the treatment of actinic keratoses on the face or scalp.	November 2013
To submit the final study report for study X-03016-3284 investigating the long term effect of Aldara in the treatment of actinic keratoses on the face or scalp with respect to the risk of progression to in-situ and invasive squamous cell carcinoma.	March 2016

PSUR submission

On the basis of the safety data submitted, the CHMP considered that the PSUR submission schedule should follow the PSUR schedule for the reference product (Aldara, imiquimod 5%), which currently is on a 3-yearly cycle.

The next data lock point for the reference medicinal product is 26 January 2014.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

Benefits

Beneficial effects

Compared to Aldara (5% imiquimod), Zyclara has lower concentration of the active substance (3.75% imiquimod), allowing the treatment of areas larger than 25 cm^2 and a higher number of lesions. The daily dosing regimen with Zyclara, compared to dosing on a certain number of days in the week for Aldara, is more intuitive and more easily followed by patients potentially improving compliance with treatment.

Data from pivotal trials have established superior short term efficacy compared to placebo. The average response rate across the 4 pivotal studies was approximately 35% for Zyclara, compared to 5% for placebo. All results were highly statistically significant.

Uncertainty in the knowledge about the beneficial effects

Although efficacy and safety of Zyclara versus placebo at the given strength and proposed posology was demonstrated through 2 pivotal trials, comparative efficacy of Aldara and Zyclara is less clear, as the 2 have never been compared in head to head trials. The efficacy and safety of Zyclara vs a well established first line treatment has never been assessed and such comparison is limited to the use of historical data which has known limitations. However, as long as Zyclara remains a second line therapy, as is the case with the reference product, Aldara, this approach (comparison vs placebo only) can be acceptable.

Risks

Unfavourable effects

The clinical safety of Zyclara is comparable to that of the reference product (Aldara 5% cream) in the treatment of actinic keratosis, which is well-established and includes local skin reactions as well as flu-like systemic signs and symptoms (fatigue, nausea, fever, myalgias, arthralgias, and chills) attributable to local cytokine release from the immune-stimulatory action of imiquimod.

The long-term safety aspect was assessed during study GW01-0803 which was a one year observational follow-up to Studies GW01-0702, GW01-0703, GW01-0704, and GW01-0705. During this follow-up study, basal cell carcinoma and squamous cell carcinoma were the most frequently reported AEs in the study. Squamous cell or basal cell carcinomas were reported in 4 patients in the 3.75% imiquimod, 3-week treatment cycle regimen and basal cell carcinoma was reported in 1 patient in the 2.5% imiquimod, 2-week treatment cycle regimen. Three out of 4 of these patients had a reported history of basal cell or squamous cell carcinoma. On 3 occasions, the investigators' assessment of causality was 'not related' to study medication and on 1 occasion 'probably not related'. These results are not alarming and, given that they occurred within weeks to months after the treatment was stopped, it is unlikely the development of squamous cell carcinoma is causally related to slightly higher systemic exposure seen with Zyclara.

Uncertainty in the knowledge about the unfavourable effects

Compared to Aldara 5% cream 2 sachets applied 3 times per week, around 20% higher systemic exposure is expected with Zyclara. The relative systemic exposure is approximately 3 times higher when Zyclara is compared to Aldara 1 sachet applied 3 times per week. According to the European SmPC of Aldara, the most clinically serious adverse event reported following accidental ingestion of 200 mg (content of approximately 21 sachets of Zyclara) was hypotension which resolved following oral or intravenous fluid administration. Therefore, despite relatively higher exposure compared to Aldara, the overall systemic exposure with Zyclara does not seem excessive.

These findings, in conjunction with safety findings from submitted clinical trials, including the one year observational study GW01-0803, indicate that the higher systemic exposure with Zyclara does not lead to major safety concerns. However, lack of data on long-term exposure (beyond the duration of the submitted clinical trials) limits the ability to detect differences in the rates of uncommon AEs compared to Aldara. In view of uncertainties with regard to the rates of progression to squamous cell carcinoma, long-term data on recurrence of actinic keratosis and progression to squamous cell carcinoma, the applicant has agreed to include the two studies X-03016-3271 and X-03016-3284, implemented as part of the Aldara (imiquimod 5%) RMP, in the RMP for Zyclara to gather long-term data on recurrences of actinic keratosis and progression to superficial squamous cell carcinoma.

Benefit-risk balance

Overall, the data presented show that Zyclara 3.75% (imiquimod) is an effective treatment for actinic keratosis. The use of Zyclara over the duration of the presented clinical trials did not raise safety issues. Compared to Aldara, the posology of Zyclara is easier to follow, potentially improving compliance. It also allows for treating a larger surface area and, therefore, higher number of lesions. The Benefit/Risk of Zyclara is considered to be favourable.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zyclara in the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic, visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults, when other topical treatment options are contraindicated or less appropriate is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMA

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states.

Not applicable.