SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALDARA 5%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each sachet contains 12.5 mg of imiquimod in 250 mg cream (5 %).
100 mg of cream contains 5 mg of imiquimod.

Excipients with known effects:
Methyl hydroxybenzoate (E218)
Propyl hydroxybenzoate (E216)
Cetyl alcohol
Stearyl alcohol
Benzyl alcohol
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream.
White to slightly yellow cream with uniform appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imiquimod cream is indicated for the topical treatment of :

- External genital and perianal warts (condylomata acuminata) in adults.
- superficial basal cell carcinoma in adults with normal immune systems when surgical methods are less appropriate.
- actinic keratoses in adults with normal immune systems.

4.2 Posology and method of administration

Posology

The application frequency and duration of treatment with imiquimod cream is different for each indication.

<u>External genital warts in adults:</u>
Imiquimod cream should be applied 3 times per week (example: Monday, Wednesday, and Friday; or Tuesday, Thursday, and Saturday) prior to normal sleeping hours, and should remain on the skin for 6 to 10 hours. Imiquimod cream treatment should continue until the clearance of visible genital or perianal warts for a maximum of 16 weeks per episode of warts.
For quantity to be applied see 4.2 Method of administration.

Superficial basal cell carcinoma in adults:
Apply imiquimod cream for 6 weeks, 5 times per week (example: Monday to Friday) prior to normal sleeping hours, and leave on the skin for approximately 8 hours.
For quantity to be applied see 4.2 Method of administration.

Actinic keratosis in adults
Treatment should be initiated and monitored by a physician. Imiquimod cream should be applied 3 times per week (example: Monday, Wednesday and Friday) for four weeks prior to normal sleeping hours, and left on the skin for approximately 8 hours. Sufficient cream should be applied to cover the treatment area. After a 4-week treatment-free period, clearance of AKs should be assessed. If any lesions persist, treatment should be repeated for another four weeks.
The maximum recommended dose is one sachet. The maximum recommended treatment duration is 8 weeks.

An interruption of dosing should be considered if intense local inflammatory reactions occur (see section 4.4) or if infection is observed at the treatment site. In this latter case, appropriate other measures should be taken. Each treatment period should not be extended beyond 4 weeks due to missed doses or rest periods.

If the treated lesion(s) show an incomplete response at the follow-up examination at 4-8 weeks after the second treatment period, a different therapy should be used (see section 4.4)

Information applicable to all indications:
If a dose is missed, the patient should apply the cream as soon as he/she remember and then he/she should continue with the regular schedule. However the cream should not be applied more than once a day.

Paediatric patients
Use in the paediatric patient population is not recommended. There are no data available on the use of imiquimod in children and adolescents in the approved indications.
Aldara should not be used in children with molluscum contagiosum due to lack of efficacy in this indication (see section 5.1).

Method of administration

External genital warts:
Imiquimod cream should be applied in a thin layer and rubbed on the clean wart area until the cream vanishes. Only apply to affected areas and avoid any application on internal surfaces. Imiquimod cream should be applied prior to normal sleeping hours. During the 6 to 10 hour treatment period, showering or bathing should be avoided. After this period, it is essential that imiquimod cream is removed with mild soap and water. Application of an excess of cream or prolonged contact with the skin may result in a severe application site reaction (see sections 4.4, 4.8 and 4.9). A single-use sachet is sufficient to cover a wart area of 20 cm^2 (approx. 3 $inches_2$). Sachets should not be re-used once opened. Hands should be washed carefully before and after application of cream.
Uncircumcised males treating warts under the foreskin should retract the foreskin and wash the area daily (see section 4.4).

Superficial basal cell carcinoma:
Before applying imiquimod cream, patients should wash the treatment area with mild soap and water and dry thoroughly. Sufficient cream should be applied to cover the treatment area, including one centimetre of skin surrounding the tumour. The cream should be rubbed into the treatment area until the cream vanishes. The cream should be applied prior to normal sleeping hours and remain on the skin for approximately 8 hours. During this period, showering and bathing should be avoided. After this period it is essential that imiquimod cream is removed with mild soap and water. Sachets should not be re-used once opened. Hands should be washed carefully before and after application of cream.

Response of the treated tumour to imiquimod cream should be assessed 12 weeks after the end of treatment. If the treated tumour shows an incomplete response, a different therapy should be used (see section 4.4).

A rest period of several days may be taken (see section 4.4) if the local skin reaction to imiquimod cream causes excessive discomfort to the patient, or if infection is observed at the treatment site. In this latter case, appropriate other measures should be taken.

Actinic keratosis:
Before applying imiquimod cream, patients should wash the treatment area with mild soap and water and dry thoroughly. Sufficient cream should be applied to cover the treatment area. The cream should be rubbed into the treatment area until the cream vanishes. The cream should be applied prior to normal sleeping hours and remain on the skin for approximately 8 hours. During this period, showering and bathing should be avoided. After this period it is essential that imiquimod cream is removed with mild soap and water. Sachets should not be re-used once opened. Hands should be washed carefully before and after application of cream.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and special precautions for use

External genital warts, superficial basal cell carcinoma and actinic keratosis:
Avoid contact with the eyes, lips and nostrils.

Imiquimod has the potential to exacerbate inflammatory conditions of the skin.

Imiquimod cream should be used with caution in patients with autoimmune conditions (refer to section 4.5). Consideration should be given to balancing the benefit of imiquimod treatment for these patients with the risk associated with a possible worsening of their autoimmune condition.

Imiquimod cream should be used with caution in organ transplant patients (refer to section 4.5). Consideration should be given to balancing the benefit of imiquimod treatment for these patients with the risk associated with the possibility of organ rejection or graft-versus-host disease.

Imiquimod cream therapy is not recommended until the skin has healed after any previous drug or surgical treatment. Application to broken skin could result in increased systemic absorption of imiquimod leading to a greater risk of adverse events (refer to section 4.8 and 4.9)

The use of an occlusive dressing is not recommended with imiquimod cream therapy.

The excipients methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216) may cause allergic reactions (possibly delayed). Cetyl alcohol and stearyl alcohol may cause local skin reactions (e.g. contact dermatitis). Benzyl alcohol may cause allergic reactions and mild local irritation.

Rarely, intense local inflammatory reactions including skin weeping or erosion can occur after only a few applications of imiquimod cream. Local inflammatory reactions may be accompanied, or even preceded, by flu-like systemic signs and symptoms including malaise, pyrexia, nausea, myalgias and rigor. An interruption of dosing should be considered.

Imiquimod should be used with caution in patients with reduced haematologic reserve (refer to section 4.8d).

External genital warts:
There is limited experience in the use of imiquimod cream in the treatment of men with foreskin-associated warts. The safety database in uncircumcised men treated with imiquimod cream three times weekly and carrying out a daily foreskin hygiene routine is less than 100 patients. In other studies, in which a daily foreskin hygiene routine was not followed, there were two cases of severe phimosis and one case of stricture leading to circumcision. Treatment in this patient population is therefore recommended only in men who are able or willing to follow the daily foreskin hygiene routine. Early signs of stricture may include local skin reactions (e.g. erosion, ulceration, oedema, induration), or increasing difficulty in retracting the foreskin. If these symptoms occur, the treatment should be stopped immediately. Based on current knowledge, treating urethral, intra-vaginal, cervical, rectal or intra-anal warts is not recommended. Imiquimod cream therapy should not be initiated in tissues where open sores or wounds exist until after the area has healed.

Local skin reactions such as erythema, erosion, excoriation, flaking and oedema are common. Other local reactions such as induration, ulceration, scabbing, and vesicles have also been reported. Should an intolerable skin reaction occur, the cream should be removed by washing the area with mild soap and water. Treatment with imiquimod cream can be resumed after the skin reaction has moderated. The risk of severe local skin reactions may be increased when imiquimod is used at higher than recommended doses (see section 4.2). However, in rare cases severe local reactions that have required treatment and/or caused temporary incapacitation have been observed in patients who have used imiquimod according to the instructions. Where such reactions have occurred at the urethral meatus, some women have experienced difficulty in urinating, sometimes requiring emergency catheterization and treatment of the affected area.

No clinical experience exists with imiquimod cream immediately following treatment with other cutaneously applied drugs for treatment of external genital or perianal warts. Imiquimod cream should be washed from the skin before sexual activity. Imiquimod cream may weaken condoms and diaphragms, therefore concurrent use with imiquimod cream is not recommended. Alternative forms of contraception should be considered.

In immunocompromised patients, repeat treatment with imiquimod cream is not recommended.

While limited data have shown an increased rate of wart reduction in HIV positive patients, imiquimod cream has not been shown to be as effective in terms of wart clearance in this patient group.

Superficial basal cell carcinoma:
Imiquimod has not been evaluated for the treatment of basal cell carcinoma within 1 cm of the eyelids, nose, lips or hairline.

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. 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. If required by the patient's discomfort or the severity 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 clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 12 weeks after the end of treatment.

No clinical experience exists with the use of imiquimod cream in immunocompromised patients.

No clinical experience exists in patients with recurrent and previously treated BCCs, therefore use for previously treated tumours is not recommended.

Data from an open label clinical trial suggest that large tumours (>7.25 cm_2) are less likely to respond to imiquimod therapy.

The skin surface area treated should be protected from solar exposure.

Actinic keratosis
Lesions clinically atypical for AK or suspicious for malignancy should be biopsied to determine appropriate treatment.

Imiquimod has not been evaluated for the treatment of actinic keratoses on the eyelids, the inside of the nostrils or ears, or the lip area inside the vermilion border.

There is very limited data available on the use of imiquimod for the treatment of actinic keratoses in anatomical locations other than the face and scalp. The available data on actinic keratosis on the forearms and hands do not support efficacy in this indication and therefore such use is not recommended.

Imiquimod is not recommended for the treatment of AK lesions with marked hyperkeratosis or hypertrophy as seen in cutaneous horns.

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. 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. 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.

Each treatment period should not be extended beyond 4 weeks due to missed doses or rest periods.

The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 4-8 weeks after the end of treatment.

No clinical experience exists with the use of imiquimod cream in immunocompromised patients.

Information on re-treating actinic keratoses lesions that have cleared after one or two courses of treatment and subsequently recur, is given in section 4.2 and 5.1.

Data from an open-label clinical trial suggest that subjects with more than 8 AK lesions showed a decreased rate of complete clearance compared to patients with less than 8 lesions.

The skin surface area treated should be protected from solar exposure.

4.5 Interaction with other medicinal products and other forms of interaction

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 immunostimulant properties, imiquimod cream should be used with caution in patients who are receiving immunosuppressive medication (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
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 (see 5.3). Caution should be exercised when prescribing to pregnant women.

Breast-feeding
As no quantifiable levels (>5 ng/ml) of imiquimod are detected in the serum after single and multiple topical doses, no specific advice can be given on whether to use or not in lactating mothers.

4.7 Effects on ability to drive and use machines

Aldara cream has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) General Description:

External genital warts:
In the pivotal trials with 3 times a week dosing, the most frequently reported adverse drug reactions judged to be probably or possibly related to imiquimod cream treatment were application site reactions at the wart treatment site (33.7% of imiquimod treated patients). Some systemic adverse reactions, including headache (3.7%), influenza-like symptoms (1.1%), and myalgia (1.5%) were also reported.

Patient reported adverse reactions from 2292 patients treated with imiquimod cream in placebo controlled and open clinical studies are presented below. These adverse events are considered at

least possibly causally related to treatment with imiquimod.

Superficial basal cell carcinoma:
In trials with 5 times per week dosing 58% of patients experienced at least one adverse event. The most frequently reported adverse events from the trials judged probably or possibly related to imiquimod cream are application site disorders, with a frequency of 28.1%. Some systemic adverse reactions, including back pain (1.1%) and influenza-like symptoms (0.5%) were reported by imiquimod cream patients.

Patient reported adverse reactions from 185 patients treated with imiquimod cream in placebo controlled phase III clinical studies for superficial basal cell carcinoma are presented below. These adverse events are considered at least possibly causally related to treatment with imiquimod.

Actinic keratosis
In the pivotal trials with 3 times per week dosing for up to 2 courses each of 4 weeks, 56% of imiquimod patients reported at least one adverse event. The most frequently reported adverse event from these trials judged probably or possibly related to imiquimod cream was application site reactions (22% of imiquimod treated patients). Some systemic adverse reactions, including myalgia (2%) were reported by imiquimod treated patients.

Patient reported adverse reactions from 252 patients treated with imiquimod cream in vehicle controlled phase III clinical studies for actinic keratosis are presented below. These adverse events are considered at least possibly causally related to treatment with imiquimod.

b) Tabular Listing of adverse events:
Frequencies are defined as Very common (1/10), Common (1/100 to <1/10) and Uncommon (1/1,000 to <1/100). Lower frequencies from clinical trials are not reported here.

	External genital warts (3x/ wk,16wks) N = 2292	**Superficial basal cell carcinoma (5x/wk, 6 wks) N = 185**	**Actinic keratosis (3x/wk, 4 or 8 wks) N = 252**
Infections and infestations:			
Infection	Common	Common	Uncommon
Pustules		Common	Uncommon
Herpes simplex	Uncommon		
Genital candidiasis	Uncommon		
Vaginitis	Uncommon		
Bacterial infection	Uncommon		
Fungal infection	Uncommon		
Upper respiratory tract infection	Uncommon		
Vulvitis	Uncommon		
Rhinitis			Uncommon
Influenza			Uncommon
Blood and lymphatic system disorders:			
Lymphadenopathy	Uncommon	Common	Uncommon
Metabolism and nutrition disorders:			

Anorexia	Uncommon		Common
Psychiatric disorders:			
Insomnia	Uncommon		
Depression	Uncommon		Uncommon
Irritability		Uncommon	
Nervous system disorders:			
Headache	Common		Common
Paraesthesia	Uncommon		
Dizziness	Uncommon		
Migraine	Uncommon		
Somnolence	Uncommon		
Eye disorders			
Conjunctival irritation			Uncommon
Eyelid oedema			Uncommon
Ear and labyrinth disorders:			
Tinnitus	Uncommon		
Vascular disorders:			
Flushing	Uncommon		
Respiratory, thoracic and mediastinal disorders:			
Pharyngitis	Uncommon		
Rhinitis	Uncommon		
Nasal congestion			Uncommon
Pharyngo laryngeal pain			Uncommon
Gastrointestinal disorders:			
Nausea	Common	Uncommon	Common
Abdominal pain	Uncommon		
Diarrhoea	Uncommon		Uncommon
Vomiting	Uncommon		
Rectal disorder	Uncommon		
Rectal tenesmus	Uncommon		
Dry mouth		Uncommon	
Skin and subcutaneous tissue			
Pruritus	Uncommon		
Dermatitis	Uncommon	Uncommon	
Folliculitis	Uncommon		
Rash erythematous	Uncommon		
Eczema	Uncommon		
Rash	Uncommon		
Sweating increased	Uncommon		
Urticaria	Uncommon		
Actinic keratosis			Uncommon
Erythema			Uncommon
Face oedema			Uncommon
Skin ulcer			Uncommon
Musculoskeletal and connective Tissue disorders:			

Myalgia	Common		Common
Arthralgia	Uncommon		Common
Back pain	Uncommon	Common	
Pain in extremity			Uncommon
Renal and urinary disorders:			
Dysuria	Uncommon		
Reproductive system and breast disorders:			
Genital pain male	Uncommon		
Penile disorder	Uncommon		
Dyspareunia	Uncommon		
Erectile dysfunction	Uncommon		
Uterovaginal prolapse	Uncommon		
Vaginal pain	Uncommon		
Vaginitis atrophic	Uncommon		
Vulval disorder	Uncommon		
General disorders and administration site conditions:			
Application site pruritus	Very common	Very common	Very common
Application site pain	Very common	Common	Common
Application site burning	Common	Common	Common
Application site irritation	Common	Common	Common
Application site erythema		Common	Common
Application site reaction			Common
Application site bleeding		Common	Uncommon
Application site papules		Common	Uncommon
Application site paraesthesia		Common	Uncommon
Application site rash		Common	
Fatigue	Common		Common
Pyrexia	Uncommon		Uncommon
Influenza-like illness	Uncommon	Uncommon	
Pain	Uncommon		
Asthenia	Uncommon		Uncommon
Malaise	Uncommon		
Rigors	Uncommon		Uncommon
Application site dermatitis			Uncommon
Application site discharge		Uncommon	Uncommon
Application site hyperaesthesia			Uncommon
Application site inflammation		Uncommon	
Application site oedema		Uncommon	Uncommon
Application site scabbing		Uncommon	Uncommon
Application site scar			Uncommon
Application site skin breakdown		Uncommon	
Application site swelling		Uncommon	Uncommon
Application site ulcer			Uncommon
Application site vesicles		Uncommon	Uncommon
Application site warmth			Uncommon

Lethargy		Uncommon	
Discomfort			Uncommon
Inflammation			Uncommon

c) Frequently occurring adverse events:

External genital warts:
Investigators of placebo controlled trials were required to evaluate protocol mandated clinical signs (skin reactions). These protocol mandated clinical sign assessments indicate that local skin reactions including erythema (61%), erosion (30%), excoriation/flaking/scaling (23%) and oedema (14%) were common in these placebo controlled clinical trials with imiquimod cream applied three times weekly (see section 4.4). Local skin reactions, such as erythema, are probably an extension of the pharmacologic effects of imiquimod cream.

Remote site skin reactions, mainly erythema (44%), were also reported in the placebo controlled trials. These reactions were at non-wart sites which may have been in contact with imiquimod cream. Most skin reactions were mild to moderate in severity and resolved within 2 weeks of treatment discontinuation. However, in some cases these reactions have been severe, requiring treatment and/or causing incapacitation. In very rare cases, severe reactions at the urethral meatus have resulted in dysuria in women (see section 4.4).

Superficial basal cell carcinoma:
Investigators of the placebo controlled clinical trials were required to evaluate protocol mandated clinical signs (skin reactions). These protocol mandated clinical sign assessments indicate that severe erythema (31%) severe erosions (13%) and severe scabbing and crusting (19%) were very common in these trials with imiquimod cream applied 5 times weekly. Local skin reactions, such as erythema, are probably an extension of the pharmacologic effect of imiquimod cream.

Skin infections during treatment with imiquimod have been observed. While serious sequelae have not resulted, the possibility of infection in broken skin should always be considered.

Actinic keratosis
In clinical trials of imiquimod cream 3 times weekly for 4 or 8 weeks the most frequently occurring application site reactions were itching at the target site (14%) and burning at the target site (5%). Severe erythema (24%) and severe scabbing and crusting (20%) were very common. Local skin reactions, such as erythema, are probably an extension of the pharmacologic effect of imiquimod cream. See 4.2 and 4.4 for information on rest periods.

Skin infections during treatment with imiquimod have been observed. While serious sequelae have not resulted, the possibility of infection in broken skin should always be considered.

d) Adverse events applicable to all indications:
Reports have been received of localized hypopigmentation and hyperpigmentation following imiquimod cream use. Follow-up information suggests that these skin color changes may be permanent in some patients. In a follow-up of 162 patients five years after treatment for sBCC a mild hypopigmentation was observed in 37% of the patients and a moderate hypopigmentation was observed in 6% of the patients. 56% of the patients have been free of hypopigmentation; hyperpigmentation has not been reported.

Clinical studies investigating the use of imiquimod for the treatment of actinic keratosis have detected a 0.4% (5/1214) frequency of alopecia at the treatment site or surrounding area. Post-marketing reports of suspected alopecia occurring during the treatment of sBCC and EGW have been received.

Reductions in hemoglobin, white blood cell count, absolute neutrophils and platelets have been observed in clinical trials. These reductions are not considered to be clinically significant in patients with normal hematologic reserve. Patients with reduced hematologic reserve have not been studied in clinical trials. Reductions in hematological parameters requiring clinical intervention have been reported from post marketing experience. There have been post marketing reports of elevated liver enzymes.

Rare reports have been received of exacerbation of autoimmune conditions.

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

e) Pediatric patients:
Imiquimod was investigated in controlled clinical studies with pediatric patients (see sections 4.2 and 5.1). There was no evidence for systemic reactions. Application site reactions occurred more frequently after imiquimod than after vehicle, however, incidence and intensity of these reactions were not different from that seen in the licensed indications in adults. There was no evidence for serious adverse reactions caused by imiquimod in pediatric patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form :
https://sideeffects.health.gov.il

4.9 Overdose

When applied topically, systemic overdosage with imiquimod cream is unlikely due to minimal percutaneous absorption. Studies in rabbits reveal a dermal lethal dose of greater than 5 g/kg. Persistent dermal overdosing of imiquimod cream could result in severe local skin reactions. Following accidental ingestion, nausea, emesis, headache, myalgia and fever could occur after a single dose of 200 mg imiquimod which corresponds to the content of approximately 16 sachets. The most clinically serious adverse event reported following multiple oral doses of ≥200 mg was hypotension which resolved following oral or intravenous fluid administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Chemotherapeutics for topical use, antivirals: ATC Code: D06BB10.

Imiquimod is an immune response modifier. Saturable binding studies suggest 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 antitumor 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.

External genital warts:

Clinical Efficacy

The results of 3 phase III pivotal efficacy studies showed that treatment with imiquimod for sixteen weeks was significantly more effective than treatment with vehicle as measured by total clearance of treated warts.

In 119 imiquimod-treated female patients, the combined total clearance rate was 60% as compared to 20% in 105 vehicle-treated patients (95% CI for rate difference: 20% to 61% , $p<0.001$). In those imiquimod patients who achieved total clearance of their warts, the median time to clearance was 8 weeks.

In 157 imiquimod-treated male patients, the combined total clearance rate was 23% as compared to 5% in 161 vehicle-treated patients (95%CI for rate difference: 3% to 36%, $p<0.001$). In those imiquimod patients who achieved total clearance of their warts, the median time to clearance was 12 weeks**.**

Superficial basal cell carcinoma:

Clinical efficacy:

The efficacy of imiquimod 5 times per week for 6 weeks was studied in two double-blind vehicle controlled clinical trials. Target tumors were histologically confirmed single primary superficial basal cell carcinomas with a minimum size of 0.5 cm_2 and a maximum diameter of 2 cm. Tumors located within 1 cm of the eyes, nose, mouth, ears or hairline were excluded. In a pooled analysis of these two studies, histological clearance was noted in 82% (152/185) of patients. When clinical assessment was also included, clearance judged by this composite endpoint was noted in 75% (139/185) of patients. These results were statistically significant ($p<0.001$) by comparison with the vehicle group, 3% (6/179) and 2% (3/179) respectively. There was a significant association between the intensity of local skin reactions (e.g. erythema) seen during the treatment period and complete clearance of the basal cell carcinoma.

Five -year data from a long-term open-label uncontrolled study indicate that an estimated 77.9% [95% CI (71.9%, 83.8%)] of all the subjects who initially received treatment became clinically clear and remained clear at 60 months.

Actinic keratosis:

Clinical efficacy:

The efficacy of imiquimod applied 3 times per week for one or two courses of 4 weeks, separated by a 4-week treatment-free period, was studied in two double-blind vehicle controlled clinical

trials. Patients had clinically typical, visible, discrete, non-hyperkeratotic, non-hypertrophic AK lesions on the balding scalp or face within a contiguous 25 cm_2 treatment area. 4-8 AK lesions were treated. The complete clearance rate (imiquimod minus placebo) for the combined trials was 46.1% (CI 39.0%, 53.1%).

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

Two open-label, randomised, controlled clinical trials compared the long-term effects of imiquimod with those of topical diclofenac in patients with actinic keratosis with respect to the risk of progression to in situ or invasive squamous cell carcinoma (SCC). Treatments were given as officially recommended. If the treated AK field was not completely cleared of lesions, additional treatment cycles could be started. All patients were followed-up until withdrawal or up to 3 years after randomisation. Results are emerged from a meta-analysis of both trials.
A total of 482 patients were included into the trials, of these 481 patients received study treatments, and of these 243 patients were treated with imiquimod and 238 patients with topical diclofenac. The treated AK field was located on the balding scalp or face with a contiguous area of about 40 cm^2 for both treatment groups presenting with a median number of 7 clinically typical AK lesions at baseline. There is clinical experience from 90 patients who got 3 or more imiquimod treatment cycles, 80 patients received 5 or more courses of imiquimod treatment over the 3-year study period.
Regarding the primary endpoint, histological progression, overall, 13 of 242 patients (5.4%) of the imiquimod group and 26 of 237 patients (11.0%) of the diclofenac group were found to have a histological progression to in situ or invasive SCC within 3 years, a difference of -5.6% (95% CI: -10.7% to -0.7%). Thereof 4 of 242 patients (1.7%) of the imiquimod and 7 of 237 patients (3.0%) of the diclofenac group were found to have a histological progression to invasive SCC within the 3-year period.
A total of 126 of 242 patients treated with imiquimod (52.1%) and 84 of 237 patients treated with topical diclofenac (35.4%) showed complete clinical clearance of the treated AK field at week 20 (i.e. about 8 weeks after the end of the initial treatment cycle); a difference of 16.6% (95% CI: 7.7%to 25.1%). For those patients with complete clinical clearance of the treated AK field recurrence of AK lesions was evaluated. A patient was counted as recurrent in these trials if at least one AK lesion was observed in the completely cleared field whereby a recurrent lesion could be a lesion which occurred at the same location as a formerly cleared lesion or a newly identified lesion anywhere in the treated AK field. The risk for recurrence of AK lesions in the treated field (as defined above) was 39.7% (50 of 126 patients) until month 12 for patients treated with imiquimod compared with 50.0% (42 of 84 patients) for patients treated with topical diclofenac, a difference of -10.3% (95% CI: -23.6% to 3.3%); and 66.7% (84 of 126 patients) for a treatment with imiquimod and 73.8% (62 of 84 patients) for topical diclofenac until month 36, a difference of -7.1% (95% CI: -19.0%to 5.7%).A patient with recurrent AK lesions (as defined above) in the completely cleared field had a chance of about 80% to become completely cleared again following an additional imiquimod treatment cycle compared with a chance of about 50% for a re-treatment with topical diclofenac.

Pediatric patients:
The approved indications genital warts, actinic keratosis and superficial basal cell carcinoma are conditions not generally seen within the pediatric population and were not studied.
Aldara Cream has been evaluated in four randomized, vehicle controlled, double-blind trials in children aged 2 to 15 years with molluscum contagiosum (imiquimod n = 576, vehicle n = 313).

These trials failed to demonstrate efficacy of imiquimod at any of the tested dosage regimens (3x/week for ≤16 weeks and 7x/week for ≤8 weeks).

5.2 Pharmacokinetic properties

External genital warts, superficial basal cell carcinoma and actinic keratosis:

Less than 0.9% of a topically applied single dose of radiolabelled imiquimod was absorbed through the skin of human subjects. The small amount of drug which was absorbed into the systemic circulation was promptly excreted by both urinary and faecal routes at a mean ratio of approximately 3 to 1. No quantifiable levels (>5 ng/ml) of drug were detected in serum after single or multiple topical doses.

Systemic exposure (percutaneous penetration) was calculated from recovery of carbon-14 from [14C] imiquimod in urine and faeces.

Minimal systemic absorption of imiquimod 5% cream across the skin of 58 patients with actinic keratosis was observed with 3 times per week dosing for 16 weeks. The extent of percutaneous absorption did not change significantly between the first and last doses of this study. Peak serum drug concentrations at the end of week 16 were observed between 9 and 12 hours and were 0.1, 0.2, and 1.6 ng/mL for the applications to face (12.5 mg, 1 single-use sachet), scalp (25 mg, 2 sachets) and hands/arms (75 mg, 6 sachets), respectively. The application surface area was not controlled in the scalp and hands/ arms groups. Dose proportionality was not observed. An apparent half-life was calculated that was approximately 10 times greater than the 2 hour half-life seen following subcutaneous dosing in a previous study, suggesting prolonged retention of drug in the skin. Urinary recovery was less than 0.6% of the applied dose at week 16 in these patients.

Paediatric patients:
The pharmacokinetic properties of imiquimod following single and multiple topical application in paediatric patients with molluscum contagiosum (MC) have been investigated. The systemic exposure data demonstrated that the extent of absorption of imiquimod following topical application to the MC lesional skin of the paediatric patients aged 6-12 years was low and comparable to that observed in healthy adults and adults with actinic keratosis or superficial basal cell carcinoma. In younger patients aged 2-5 years absorption, based on C_{max} values, was higher compared to adults.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, mutagenicity and teratogenicity.
In a four-month rat dermal toxicity study, significantly decreased body weight and increased spleen weight were observed at 0.5 and 2.5 mg/kg; similar effects were not seen in a four month mouse dermal study. Local dermal irritation, especially at higher doses, was observed in both species.

A two-year mouse carcinogenicity study by dermal administration on three days a week did not induce tumours at the application site. However, the incidences of hepatocellular tumours among treated animals were greater than those for controls. The mechanism for this is not known, but as imiquimod has low systemic absorption from human skin, and is not mutagenic, any risk to humans from systemic exposure is likely to be low. Furthermore, tumours were not seen at any site in a 2-year oral carcinogenicity study in rats.

Imiquimod cream was evaluated in a photocarcinogenicity bioassay in albino hairless mice exposed to simulated solar ultraviolet radiation (UVR). Animals were administered imiquimod cream three times per week and were irradiated 5 days per week for 40 weeks. Mice were maintained for an additional 12 weeks for a total of 52 weeks. Tumours occurred earlier and in greater number in the group of mice administered the vehicle cream in comparison with the low UVR control group. The significance for man is unknown. Topical administration of imiquimod cream resulted in no tumour enhancement at any dose, in comparison with the vehicle cream group.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isostearic acid, Polysorbate 60, Stearyl alcohol, White soft paraffin, Cetyl alcohol , Benzyl alcohol, Glycerol, Sorbitan stearate, Xanthan gum, Methyl hydroxybenzoate (E 218) Propyl hydroxybenzoate (E 216), Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

Sachets should not be re-used once opened.

6.5 Nature and contents of container

Boxes of 12 single-use polyester/aluminium/polyethylene sachets, containing 250 mg of cream.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Megapharm Ltd., 15 Hatidhar street, Ra'anana, Israel.

8. MARKETING AUTHORISATION NUMBER(S)

114-44-29675

9. MANUFACTURER

Kindeva Drug Delivery Ltd., Loughborough, Leicestershire, UK

10. Revised in May 2023 according to MOHs guidelines.

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