ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALDARA 5% cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 (E 218) 2.0 mg/g cream
Propyl hydroxybenzoate (E 216) 0.2 mg/g cream
Cetyl alcohol 22.0 mg/g cream
Stearyl alcohol 31.0 mg/g cream

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream.
White to slightly yellow cream.

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.
- Small superficial basal cell carcinomas (sBCCs) in adults.
- Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs) on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate.

4.2 Posology and method of administration

Posology

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

External genital warts in adults:

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 or for a maximum of 16 weeks per episode of warts.
For quantity to be applied see section 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.

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 area does not show complete clearance at a follow-up examination about 8 weeks after the last 4-weeks course of treatment, an additional 4-weeks course of Aldara treatment may be considered.

A different therapy is recommended if the treated lesion(s) shows insufficient response to Aldara.

Actinic keratosis lesions that have cleared after one or two courses of treatment and subsequently recur can be re-treated with one or two further courses of Aldara cream following an at least 12 weeks treatment pause (see section 5.1).

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 population
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 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 (E 218) and propyl hydroxybenzoate (E 216) may cause allergic reactions (possibly delayed). Cetyl alcohol and stearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

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

Imiquimod is not recommended for the treatment of 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 keratosis 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 immunostimulating 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 section 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 disorders:			
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 localised hypopigmentation and hyperpigmentation following imiquimod cream use. Follow-up information suggests that these skin colour 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. Postmarketing reports of suspected alopecia occurring during the treatment of sBCC and EGW have been received.

Reductions in haemoglobin, white blood cell count, absolute neutrophils and platelets have been observed in clinical trials. These reductions are not considered to be clinically significant in patients with normal haematologic reserve. Patients with reduced haematologic reserve have not been studied in clinical trials. Reductions in haematological parameters requiring clinical intervention have been reported from postmarketing experience. There have been postmarketing 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 postmarketing experience include erythema multiforme, Stevens Johnson syndrome and cutaneous lupus erythematosus.

e) Paediatric population:

Imiquimod was investigated in controlled clinical studies with paediatric 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 reaction caused by imiquimod in paediatric 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 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.

<u>External genital warts:</u>

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**.**

<u>Superficial basal cell carcinoma:</u>

Clinical efficacy:

The efficacy of imiquimod 5 times per week for 6 weeks was studied in two double-blind vehicle controlled clinical trials. Target tumours 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. Tumours 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, nonhyperkeratotic, nonhypertrophic 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.

Paediatric population

The approved indications genital warts, actinic keratosis and superficial basal cell carcinoma are conditions not generally seen within the paediatric population and were not studied.
Aldara Cream has been evaluated in four randomised, 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 population
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
benzyl alcohol
cetyl alcohol
stearyl alcohol
white soft paraffin
polysorbate 60
sorbitan stearate
glycerol
methyl hydroxybenzoate (E 218)
propyl hydroxybenzoate (E 216)
xanthan gum
purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.
Sachets should not be re-used once opened.

6.5 Nature and contents of container

Boxes of 12 or 24 single-use polyester/aluminium foil sachets, containing 250 mg of cream.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Meda AB
Pipers väg 2A
170 73 Solna
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/080/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18/09/1998
Date of last renewal: 03/09/2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

3M Health Care Limited, Derby Road, Loughborough, Leicester, LE11 5SF, United Kingdom.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medicinal prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Aldara 5% cream
imiquimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: isostearic acid, benzyl alcohol, cetyl alcohol, stearyl alcohol, white soft paraffin, polysorbate 60, sorbitan stearate, glycerol, methyl hydroxybenzoate (E 218), propyl hydroxybenzoate (E 216), xanthan gum, purified water.

See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Cream
12 sachets. Each containing 250 mg of cream.
24 sachets. Each containing 250 mg of cream.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Cutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only. Discard any cream remaining in a sachet after use.

8. EXPIRY DATE

Exp.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Meda AB
Box 906
170 09 Solna
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/080/001 12 sachets
EU/1/98/080/002 24 sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aldara

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET TEXT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Aldara 5% cream
Imiquimod
Cutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

Exp.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 mg cream

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Aldara 5% cream
Imiquimod

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If any get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Aldara cream is and what it is used for

Aldara cream may be used for three different conditions. Your doctor may prescribe Aldara cream for the treatment of:

- Warts (condylomata acuminata) on the surface of the genitals (sexual organs) and around the anus (back passage)

- Superficial basal cell carcinoma.
  This is a common slow-growing form of skin cancer with a very small likelihood of spread to other parts of the body. It usually occurs in middle-aged and elderly people, especially those who are fair-skinned and is caused by too much sun exposure. If left untreated, basal cell carcinoma can disfigure, especially on the face – therefore early recognition and treatment are important.

- Actinic keratosis
  Actinic keratoses are rough areas of skin found in people who have been exposed to a lot of sunshine over the course of their lifetime. Some are skin coloured, others are greyish, pink, red or brown. They can be flat and scaly, or raised, rough, hard and warty. Aldara should only be used for flat actinic keratoses on the face and scalp in patients with a healthy immune system where your doctor has decided that Aldara is the most appropriate treatment for you.

Aldara cream helps your body´s own immune system to produce natural substances which help fight your basal cell carcinoma, actinic keratosis or the virus that has caused your warts.

2. What you need to know before you use Aldara cream

Do not use Aldara cream

- if you are allergic to imiquimod or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before using Aldara cream

- If you have previously used Aldara cream or other similar preparations tell your doctor before starting this treatment.
- Tell your doctor if you have problems with your immune system.
- Do not use Aldara cream until the area to be treated has healed after previous drug or surgical treatment.
- Avoid contact with the eyes, lips and nostrils. In the event of accidental contact, remove cream by rinsing with water.
- Do not apply the cream internally.
- Do not use more cream than your doctor has advised.
- Do not cover the treated area with bandages or other dressings after you have applied Aldara cream.
- If the treated site becomes too uncomfortable, wash the cream off with mild soap and water. As soon as the problem has stopped you may restart to apply the cream.
- Tell your doctor if you have an abnormal blood count.

Because of the way Aldara works, there is a possibility that the cream may worsen existing inflammation in the treatment area.

- If you are being treated for genital warts follow these additional precautions:

  Men with warts under the foreskin should pull the foreskin back each day and wash underneath it. If not washed daily the foreskin may be more likely to show signs of tightness, swelling and wearing away of the skin and result in difficulty in pulling it back. If these symptoms occur, stop the treatment immediately and call your doctor.
  If you have open sores: do not start using Aldara cream until after the sores have healed.
  If you have internal warts: do not use Aldara cream in the urethra (the hole from which urine is passed), the vagina (birth canal), the cervix (internal female organ), or anywhere inside your anus (rectum).
  Do not use this medication for more than one course if you have problems with your immune system, either due to illness or because of the medicines you are already taking. If you think this applies to you talk to your doctor.
  If you are HIV positive you should inform your doctor as Aldara cream has not been shown to be as effective in HIV positive patients.
  If you decide to have sexual relations while you still have warts, apply Aldara cream after - not before - sexual activity. Aldara cream may weaken condoms and diaphragms, therefore the cream should not be left on during sexual activity. Remember, Aldara cream does not protect against giving HIV or other sexually transmitted diseases to someone else.

- If you are being treated for basal cell carcinoma or actinic keratosis follow these additional precautions:

  Do not use sunlamps or tanning beds, and avoid sunlight as much as possible during treatment with Aldara cream. Wear protective clothing and wide brimmed hats when outdoors.

Whilst using Aldara cream and until healed, the treatment area is likely to appear noticeably different from normal skin.

Children and adolescents

Use in children and adolescents is not recommended.

Other medicines and Aldara cream

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
There are no medicines known to be incompatible with Aldara cream.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.
You must tell your doctor if you are pregnant or intend to become pregnant. Your doctor will discuss the risks and benefits of using Aldara cream during pregnancy. Studies in animals do not indicate direct or indirect harmful effects in pregnancy.

Do not breast-feed your infant during treatment with Aldara cream, as it is not known whether imiquimod is secreted in human milk.

Driving and using machines

This medicine has no or negligible influence on the ability to drive and use machines.

Aldara cream contains methyl hydroxybenzoate, propyl hydroxybenzoate, cetyl alcohol and stearyl alcohol

Methyl hydroxybenzoate (E 218) and propyl hydroxybenzoate (E 216) may cause allergic reactions (possibly delayed). Cetyl alcohol and stearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

3. How to use Aldara cream

Children and adolescents:
Use in children and adolescents is not recommended.

Adults:
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Wash hands carefully before and after applying the cream. Do not cover the treated area with bandages or other dressings after you have applied Aldara cream.
Open a new sachet each time you use the cream. Dispose of any cream left in the sachet after use. Do not save the opened sachet for use at a later date.

The treatment frequency and duration differ for genital warts, basal cell carcinoma and actinic keratosis (see specific instructions for each indication).

- **If you are being treated for genital warts:**

Application Instructions – (Mon, Wed and Fri)
1. Before going to bed, wash your hands and the treatment area with mild soap and water. Dry thoroughly.
2. Open a new sachet and squeeze some cream onto your fingertip.
3. Apply a thin layer of Aldara cream onto clean, dry wart area and rub gently into the skin until cream vanishes.
4. After application of the cream, throw away the opened sachet and wash hands with soap and water.
5. Leave Aldara cream on the warts for 6 to 10 hours. Do not shower or bathe during this time.
6. After 6 to 10 hours wash the area where Aldara cream was applied with mild soap and water.

Apply Aldara cream 3 times per week. For example, apply the cream on Monday, Wednesday and Friday. One sachet contains enough cream to cover a wart area of 20 cm^2 (approx. 3 square inches).

Men with warts under the foreskin should pull the foreskin back each day and wash underneath it (see section 2 "Warnings and precautions")

Continue to use Aldara cream as instructed until your warts have completely gone (half the females who clear will do so in 8 weeks, half the males who clear will do so in 12 weeks but in some patients warts may clear as early as 4 weeks).

Do not use Aldara cream for more than 16 weeks in the treatment of each episode of warts.

If you have the impression that the effect of Aldara cream is too strong or too weak, talk to your doctor or pharmacist.

- **If you are being treated for basal cell carcinoma:**

Application Instructions – (Mon, Tues, Wed, Thurs and Fri)
1. Before going to bed, wash your hands and the treatment area with mild soap and water. Dry thoroughly.
2. Open a new sachet and squeeze some cream onto your fingertip.
3. Apply Aldara cream to the affected area and 1cm (approx. 0.5 inch) around the affected area. Rub gently into the skin until the cream vanishes.
4. After application of the cream, throw away the opened sachet. Wash hands with soap and water.
5. Leave Aldara cream on the skin for about 8 hours. Do not shower or bathe during this time.
6. After about 8 hours, wash the area where Aldara cream was applied with mild soap and water.

Apply sufficient Aldara cream to cover the treatment area and 1 cm (about ½ an inch) around the treatment area each day for 5 consecutive days each week for 6 weeks. For example, apply the cream from Monday to Friday. Do not apply the cream on Saturday and Sunday.

- **If you are being treated for actinic keratosis**

Application Instructions – (Mon, Wed and Fri)
1. Before going to bed, wash your hands and the treatment area with mild soap and water. Dry thoroughly.
2. Open a new sachet and squeeze some cream onto your fingertip.
3. Apply the cream to the affected area. Rub gently into the area until the cream vanishes.
4. After application of the cream, throw away the opened sachet. Wash hands with soap and water.
5. Leave Aldara cream on the skin for about 8 hours. Do not shower or bathe during this time.
6. After about 8 hours, wash the area where Aldara cream was applied with mild soap and water.

Apply Aldara cream 3 times per week. For example, apply the cream on Monday, Wednesday and Friday. One sachet contains enough cream to cover an area of 25 cm^2 (approx. 4 square inches). Continue treatment for four weeks. Four weeks after finishing this first treatment, your doctor will assess your skin. If the lesions have not all disappeared, further four weeks of treatment may be necessary.

If you use more Aldara cream than you should

Wash the extra away with mild soap and water. When any skin reaction has gone you may then continue with your treatment.

If you accidentally swallow Aldara cream please contact your doctor.

If you forget to use Aldara cream

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

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

The frequency of side effects is classified as follows:
Very common side effects (likely to occur in more than 1 in 10 patients)
Common side effects (likely to occur in fewer than 1 in 10 patients)
Uncommon side effects (likely to occur in fewer than 1 in 100 patients)
Rare side effects (likely to occur in fewer than 1 in 1,000 patients)
Very rare side effects (likely to occur in fewer than 1 in 10,000 patients).

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are using Aldara cream.
Some patients have experienced changes in skin colour in the area where Aldara cream was applied. While these changes have tended to improve with time, in some patients they may be permanent.
If your skin reacts badly when using Aldara cream, stop applying the cream, wash the area with mild soap and water and contact your doctor or pharmacist.
In some individuals a lowering of blood counts was noted. A lowering of blood counts might make you more susceptible to infections, make you bruise more easily or cause fatigue. If you notice any of these symptoms, tell your doctor.

Serious skin reactions have been reported rarely. If you experience skin lesions or spots on your skin that start out as small red areas and progress to look like mini targets, possibly with symptoms such as itching, fever, overall ill feeling, achy joints, vision problems, burning, painful or itchy eyes and mouth sores, stop using Aldara cream and tell your doctor immediately.
A small number of patients have experienced hair loss at the treatment site or surrounding area.

● <u>If you are being treated for genital warts:</u>

Many of the undesirable effects of Aldara cream are due to its local action on your skin.

Very common effects include redness (61% patients), wearing away of the skin (30% patients), flakiness and swelling. Hardening under the skin, small open sores, a crust that forms during healing, and small bubbles under the skin may also occur. You might also feel itching (32% patients), a

burning sensation (26% patients) or pain in areas where you have applied Aldara cream (8% patients). Most of these skin reactions are mild and the skin will return to normal within about 2 weeks after stopping treatment.

Commonly some patients (4% or less) have experienced headache, **uncommonly** fevers and flu like symptoms joint and muscle pains; prolapse of the womb; pain on intercourse in females; erection difficulties; increase in sweating; feeling sick; stomach and bowel symptoms; ringing in the ears; flushing; tiredness; dizziness; migraine; pins and needles; insomnia; depression; loss of appetite; swollen glands; bacterial, viral and fungal infections (e.g. cold sores); vaginal infection including thrush; cough and colds with sore throat.

Very rarely severe and painful reactions have occurred, particularly when more cream has been used than recommended. Painful skin reactions at the opening of the vagina have very rarely made it difficult for some women to pass urine. If this occurs you should seek medical help immediately.

● If you are being treated for basal cell carcinoma:

Many of the undesirable effects of Aldara cream are due to its local action on your skin. Local skin reactions can be a sign that the drug is working as intended.

Very Commonly the treated skin may be slightly itchy.

Common effects include: pins and needles, small swollen areas in the skin, pain, burning, irritation, bleeding, redness or rash.
If a skin reaction becomes too uncomfortable during treatment, speak to your doctor. He/she may advise you to stop applying Aldara cream for a few days (i.e. to have a short rest from treatment).
If there is pus (matter) or other suggestion of infection, discuss this with your doctor. Apart from reactions in the skin, other common effects include swollen glands and back pain.
Uncommonly some patients experience changes at the application site (discharge, inflammation, swelling, scabbing, skin breakdown, blisters, dermatitis) or irritability, feeling sick, dry mouth, flu-like symptoms and tiredness.

● If you are being treated for actinic keratosis

Many of the undesirable effects of Aldara cream are due to its local action on your skin. Local skin reactions can be a sign that the drug is working as intended.

Very commonly the treated skin may be slightly itchy.

Common effects include pain, burning, irritation or redness.
If a skin reaction becomes too uncomfortable during treatment, speak to your doctor. He/she may advise you to stop applying Aldara cream for a few days (i.e. to have a short rest from treatment).
If there is pus (matter) or other suggestion of infection, discuss this with your doctor. Apart from reactions in the skin, other common effects include headache, anorexia, nausea, muscle pain, joint pain and tiredness.

Uncommonly some patients experience changes at the application site (bleeding, inflammation, discharge, sensitivity, swelling, small swollen areas in the skin, pins and needles, scabbing, scarring, ulceration or a feeling of warmth or discomfort), or inflammation of the lining of the nose, stuffy nose, flu or flu-like symptoms, depression, eye irritation, swelling of the eyelid, throat pain, diarrhoea, actinic keratosis, redness, swelling of the face, ulcers, pain in extremity, fever, weakness or shivering.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aldara cream

Keep this medicine out of the sight and reach of children.

Do not store above 25 °C.

Do not use this medicine after the expiry date which is stated on the label.

Sachets should not be re-used once opened.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Aldara cream contains

- The active substance is imiquimod. Each sachet contains 250 mg cream (100 mg cream contains 5 mg imiquimod).
- The other ingredients are isostearic acid, benzyl alcohol, cetyl alcohol, stearyl alcohol, white soft paraffin, polysorbate 60, sorbitan stearate, glycerol, methyl hydroxybenzoate (E 218), propyl hydroxybenzoate (E 216), xanthan gum, purified water.

What Aldara cream looks like and contents of the pack

- Each Aldara 5% cream sachet contains 250 mg of a white to slightly yellow cream.
- Each box contains 12 or 24 single-use polyester/aluminium foil sachets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Meda AB
Pipers väg 2
170 73 Solna
Sweden

Manufacturer

3M Health Care Limited
Derby Road
Loughborough
Leicestershire
LE11 5SF, United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in (MM/YYYY).

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.