PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ALDARA, 5 % cream.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 250 mg cream sachet contains 5 % Imiquimod (12,5 mg)

Each 2,0 g cream pump contains 5 % Imiquimod (100 mg)

Preservatives: Methyl hydroxybenzoate 0,2 % *m/m*

Propyl hydroxybenzoate 0,02 % *m/m*

Benzyl alcohol 2 % *m/m*

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream. White to faintly yellow cream with a uniform appearance.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

ALDARA cream is indicated for the topical treatment of superficial basal cell carcinoma (sBCC), and of external genital/perianal warts (condyloma acuminata) and clinically typical, non-hyperkeratotic, non-hypertrophic actinic keratosis (AKs) on the face or scalp in adult patients.

4.2 Posology and method of administration

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

Information applicable to all indications:

Local skin reactions such as erythema, erosion, excoriation/flaking and oedema at the treatment site are very common. A rest period of several days may be taken if required due to the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides. Any rest periods taken by patients in the clinical studies were considered part of the treatment period. The treatment period was not extended to make up for rest periods or missed doses.

Higher than recommended doses may lead to increased local skin reactions.

Superficial Basal Cell Carcinoma

ALDARA cream should be applied once daily for 5 consecutive days per week and the treatment should continue for 6 weeks. Sufficient cream should be applied to cover the treatment area, including one centimetre of skin surrounding the tumour. The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 6 to 12 weeks after the end of treatment.

External Genital/Perianal Warts

ALDARA cream should be applied once daily, 3 times per week (every other day, followed by a 2-day treatment-free interval) prior to normal sleeping hours and should remain on the skin for 8 (6 to 10) hours. Treatment should continue until there is a clearance of visible genital/perianal warts or for a maximum of 16 weeks.

Actinic Keratosis

ALDARA cream should be applied 3 times per week (example: Monday, Wednesday and Friday) prior to normal sleeping hours, and left on the skin for approximately 8 hours.

Treatment should continue for 4 weeks. After a 4-week treatment-free period the medical practitioner should assess the treated area to determine clearance of AKs. If any AKs persist in the treatment area, treatment should continue 3 times per week for an additional 4 weeks (for a maximum total treatment duration of 8 weeks).

Clearance of Actinic Keratosis should be assessed at 4 to 8 weeks, following each treatment period.

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

Patients being treated for Superficial Basal Cell Carcinoma

1. Most patients using **ALDARA** cream for the treatment of superficial basal cell carcinoma experience erythema, oedema, induration, erosion, scabbing/crusting and flaking/scaling at the application site with normal dosing. These local skin reactions generally decrease in intensity or resolve after cessation of **ALDARA** cream therapy.
2. During treatment and until healed, affected skin is likely to appear noticeably different from normal skin.
3. It is prudent for patients to minimize or avoid exposure to natural or artificial sunlight.
4. The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 6 to 12 weeks after the end of treatment.
5. Patients should contact their doctor if they experience any signs or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult.

Patients being treated for External Genital/Perianal Warts

1. It is common for patients to experience local skin reactions such as erythema, erosion, excoriation/flaking, and oedema at the site of application or surrounding areas.

   Most skin reactions are mild to moderate. Severe skin reactions can occur and should be promptly reported to the prescribing doctor.

Should severe local skin reactions occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with **ALDARA** cream can resume after the skin reaction has subsided.

2. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin. It should be washed from the skin before sexual activity.
3. The effect of **ALDARA** cream on the transmission of genital/perianal warts is unknown. **ALDARA** cream may weaken condoms and vaginal diaphragms. Therefore, concurrent use is not recommended.
4. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.
5. Patients should be aware that new warts may develop during the therapy, as **ALDARA** cream does not cure this condition.

Patients being treated for Actinic Keratosis

1. Most patients using **ALDARA** cream for the treatment of Actinic Keratosis experience erythema, flaking/scaling/dryness and scabbing/crusting at the application site with normal dosing. These local skin reactions may be severe, but generally decrease in intensity or resolve after cessation of **ALDARA** cream therapy.
2. During treatment and until healed, affected skin is likely to appear noticeably different from normal skin.
3. It is prudent for patients to minimise or avoid exposure to natural or artificial sunlight.
4. During treatment, sub-clinical Actinic Keratosis lesions may appear in the treatment area.
5. Patients should contact their doctor if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult.

Methods of administration

Before applying **ALDARA** cream, the patient should wash the treatment area with mild soap and water, and allow the area to dry thoroughly.

ALDARA cream should be applied prior to normal sleeping hours, and should remain on the skin for 8 (6 to 10) hours.

ALDARA cream should be applied in a thin layer and rubbed on the affected area until the cream vanishes. The use of an occlusive dressing is not recommended with **ALDARA** therapy. During the 6 to 10 hours treatment period, showering or bathing should be avoided. After this period **ALDARA** cream should be removed with mild soap and water.

The cream in a single-use sachet or four actuations of the pump is sufficient to cover a wart area of 20 cm^2. Sachets are to be used only once. Sachets should not be re-used once opened. Hands should be washed carefully before and after application of **ALDARA** cream.

4.3 Contraindications

Hypersensitivity to any of the ingredients.

4.4 Special warnings and precautions for use

Paediatric use: Safety and efficacy of **ALDARA** cream in patients below the age of 18 years have not been established.

ALDARA cream has not been evaluated for treatment of internal genital warts and should not be used to treat urethral, intra-vaginal, cervical, rectal or intra-anal warts. Application of **ALDARA** cream in the vagina is considered internal and should be avoided. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can result in pain or swelling, and may cause difficulty in passing urine.

ALDARA cream has not been evaluated for the treatment of superficial basal cell carcinoma within 1 cm of the eyelids, nose or lips.

ALDARA cream should be used with caution in patients with autoimmune conditions (see **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.

ALDARA cream should be used with caution in organ transplant patients (see **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.

Due to its immunostimulating properties, **ALDARA** should be used with caution in patients who are receiving immunosuppressive medication.

Intense local inflammatory reactions including skin weeping or erosion have occurred 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.

Should an intolerable reaction occur, the cream should be removed by washing the area with mild soap and water.

Treatment with **ALDARA** cream can be resumed after the skin reaction has moderated. Any rest periods taken by patients in the clinical studies were considered to be part of the treatment period.

The treatment period was not extended to make up for rest periods or missed doses.

Uncircumcised males with warts under the foreskin should retract the foreskin and wash the area daily.

Where **ALDARA** cream is used for the treatment of external genital/perianal warts, it should be washed from the skin before sexual activity. **ALDARA** cream may weaken condoms and diaphragms; therefore, concurrent use with **ALDARA** cream is not recommended.

ALDARA, as an immune response modifier, has been shown to induce mRNA for IL-8 and has the potential to exacerbate inflammatory conditions of the skin.

Actinic Keratosis

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

During therapy and until healed, affected skin is likely to appear noticeably different from normal skin. Severe local skin reactions are very common but these reactions generally decrease in intensity during therapy or resolve after cessation of **ALDARA** 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 intensity of the local skin reaction, a rest period of several days may be taken. However, there is a decreased efficacy if too many doses are missed. Treatment with **ALDARA** 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 to 8 weeks after the end of treatment.

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

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

No clinical experience exists with **ALDARA** cream immediately following treatment with other cutaneously-applied medicines for treatment of external genital and perianal warts. Therefore, **ALDARA** cream for such patients is not recommended until the skin has healed from any previous medical or surgical treatment.

eports have been received of localised hypopigmentation and hyperpigmentation following **ALDARA** use. Follow-up information suggests that these skin-colour changes may be permanent.

Methyl hydroxybenzoate and propyl hydroxybenzoate may cause allergic reaction (possibly delayed).

4.5 Interaction with other medicines and other forms of interaction

Interactions with other medicines, including immunosuppressive medicines, have not been studied; such interactions with systemic medicines would be limited by the percutaneous absorption of **ALDARA** cream. Due to its immunostimulating properties, **ALDARA** should be used with caution in patients who are receiving immunosuppressive medicines (see **4.4**).

4.6 Fertility, pregnancy and lactation

ALDARA cream is not recommended for use during pregnancy and lactation as safety has not been demonstrated.

4.7 Effects on ability to drive and use machines

Unknown.

4.8 Undesirable effects

The pharmacological action of **ALDARA** cream may give rise to certain expected effects (see table below).

Actinic Keratosis

Apart from the local skin reactions mentioned below, the most frequently occurring application site reactions were itching at the target site (14 %) and burning at the target site (5 %).

Investigators of the vehicle controlled clinical trials were required to evaluate protocol mandated clinical signs (local skin reactions). These protocol mandated clinical sign assessments indicate that severe erythema (24 %) and severe scabbing and crusting (20 %) were very common in these trials with **ALDARA** cream applied 3x weekly for 4 to 8 weeks. Local sign reactions, such as erythema, are probably an extension of the pharmacologic effect of **ALDARA** cream. (Refer to **4.2**)

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

Side effects

Side effects are listed below in CIOMS frequency categories as follows:

Very common: Greater than 10 %

Common: 1 – 10 %

Uncommon: 0,1 – 1 %

	External Genital Warts	**Superficial Basal Cell Carcinoma**	**Actinic Keratosis**
	Imiquimod 3 x per week, 16 weeks	**Imiquimod 5 x per week, 6 weeks**	**Imiquimod 3 x per week, 4 or 8 weeks**
Infections and infestations:			
Bacterial infections	Uncommon		
Fungal infections	Uncommon		
Genital candidiasis	Uncommon		
Herpes Simplex	Uncommon		
Infection	Common	Common	Uncommon
Influenza			Uncommon

Pustules		Common	Uncommon
Rhinitis			Uncommon
Upper respiratory tract infections	Uncommon		
Vaginitis	Uncommon		
Vulvitis	Uncommon		
Blood and lymphatic system disorders:			
Lymphadenopathy	Uncommon	Common	Uncommon
Metabolism and nutrition disorders:			
Anorexia	Uncommon		Common
Psychiatric disorders:			
Depression	Uncommon		Uncommon
Insomnia	Uncommon		
Irritability		Uncommon	
Nervous system disorders:			
Dizziness	Uncommon		
Headache	Common	Common**	Common
Migraine	Uncommon		
Paraesthesia	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:			
Nasal congestion			Uncommon
Pharyngitis	Uncommon		
Pharyngo laryngeal pain			Uncommon
Rhinitis	Uncommon		
Gastrointestinal disorders:			
Abdominal pain	Uncommon		
Diarrhoea	Uncommon		Uncommon
Dry mouth		Uncommon	
Nausea	Common	Uncommon	Common
Rectal disorder	Uncommon		
Rectal tenesmus	Uncommon		
Vomiting	Uncommon		

Skin and subcutaneous tissue disorders:			
Actinic keratosis			Uncommon
Dermatitis	Uncommon	Uncommon	
Eczema	Uncommon		
Erythema			Uncommon
Face oedema			Uncommon
Folliculitis	Uncommon		
Pruritus	Uncommon		Uncommon
Rash	Uncommon		
Rash erythematous	Uncommon		
Skin ulcer			Uncommon
Sweat increases	Uncommon		
Urticaria	Uncommon		
Musculoskeletal and connective tissue disorders:			
Arthralgia	Uncommon		Common
Back pain	Uncommon	Common	
Myalgia	Common		Common
Pain in extremity			Uncommon
Renal and urinary disorders:			
Dysuria	Uncommon		
Reproductive system and breast disorders:			
Dyspareunia	Uncommon		
Erectile dysfunction	Uncommon		
Genital pain male	Uncommon		
Penile disorders	Uncommon		
Uterovaginal prolapse	Uncommon		
Vaginal pain	Uncommon		
Vaginitis atrophic	Uncommon		
Vulval disorder	Uncommon		
General disorders and administration site conditions:			
Application Site Disorders: Target site			
Bleeding		Common	Uncommon
Burning*	Very common	Very common	Very common
Dermatitis			Uncommon
Discharge		Uncommon	Uncommon
Erythema		Common	Common
Hyperaesthesia: Hypopigmentation Inflammation Irritation	 Common* Common*	 Uncommon Common	 Common

Oedema		Uncommon	Uncommon
Pain	Common*	Common	Common
Papules		Common	Uncommon
Paraesthesia		Common	Uncommon
Pruritis/Itching	Very common*	Very common	Very Common
Rash	Common*	Common	
Reaction			Common
Scabbing		Uncommon	Uncommon
Scar			Uncommon
Sensitive	Common*		
Skin breakdown		Uncommon	
Sore	Common*		
Stinging sensation	Common*		
Swelling		Uncommon	Uncommon
Tenderness	Common*	Common	
Ulcer			Uncommon
Vesicles		Uncommon	Uncommon
Warmth			Uncommon
Application Site Disorder: Remote site			
Burning	Common*		
Erythema		Common	
Itching/Pruritus	Common*		
Pain	Common*		
Tenderness	Common		
Asthenia	Uncommon		Uncommon
Discomfort			Uncommon
Fatigue	Common	Common	Common
Inflammation			Uncommon
Influenza like illness	Uncommon	Uncommon	
Lethargy		Uncommon	
Malaise	Uncommon		
Pain	Uncommon	Uncommon	
Pyrexia/Fever	Uncommon	Common	Uncommon
Rigors	Uncommon		Uncommon

**AEs reported from 273 patients*

***Incidences reported without regard to causality with Aldara cream*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. Alternately you can contact iNova Pharmaceuticals (Pty) Ltd at +27 11 087 0000. Website: www.inovapharma.co.za.

4.9 Overdose

When applied topically, systemic overdosage with **ALDARA** cream is unlikely due to minimal percutaneous absorption. Animal studies reveal a dermal lethal dose of greater than 5 000 mg/kg.

Persistent dermal overdosing of **ALDARA** cream could result in severe local reactions. Discontinuation of use of **ALDARA** cream is followed by healing of local skin reactions within 2 weeks.

Following accidental ingestion, nausea, emesis, headache, myalgia and fever could occur after a single dose of 200 mg imiquimod. This corresponds to the content of approximately 16 sachets or 3 pumps. Treatment is symptomatic and supportive. 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

A 34 Other

Imiquimod is an immune response modifier that is not a nucleoside analogue. Saturable binding studies suggest that a membrane receptor for imiquimod exists on responding cells. In animal models imiquimod has indirect antiviral and antitumour properties. Its activity is principally related to induction of alpha interferon, but other cytokines are also involved. The exact mechanism of action is unknown.

Imiquimod induces a local immune response and a decrease in HPV-DNA for genotypes 6 and 11 in patients being treated for external genital/perianal warts. The immune response is characterized by significant increases in mRNA for IFN-alpha, 2'5'-AS and IFN-gamma in wart tissue. As such, the mechanism is believed to be secondary to cell-mediated immunity.

5.2 Pharmacokinetic properties

Less than 0,9 % of topically applied single dose of radiolabelled imiquimod was absorbed through the skin of human subjects. The small amount of imiquimod which was absorbed into the systemic circulation was promptly excreted by both urinary and faecal routes at a mean ratio of 3:1. No quantifiable levels were detected in serum after single or multiple topical dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- cetyl alcohol
- glycerol
- isostearic acid
- polysorbate 60
- purified water
- sorbitan monostearate
- stearyl alcohol
- white soft paraffin
- xanthan gum

6.2 Incompatibilities

Unknown

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN

The content of the pump should be used 4 weeks after opening and the pump discarded thereafter.

6.5 Nature and contents of container

ALDARA cream is available in boxes containing 3 and 12 single use polyester/aluminium foil sachets or in a pack containing 1 or 2 pumps.

Four (4) actuations of the pump is approximately equivalent to one (1) 250 mg sachet of **ALDARA** cream.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

32/34/0541.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/05/1999.

10 DATE OF REVISION OF THE TEXT

10 August 2007.

19 February 2020