ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zyclara 3.75% cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 9.375 mg of imiquimod in 250 mg cream (3.75%).
Each gram of cream contains 37.5 mg of imiquimod.

Excipients with known effects:
Methyl parahydroxybenzoate (E 218) 2.0 mg/g cream
Propyl parahydroxybenzoate (E 216) 0.2 mg/g cream
Cetyl alcohol 22.0 mg/g cream
Stearyl alcohol 31.0 mg/g cream
Benzyl alcohol 20.0 mg/g cream

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 indications

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

4.2 Posology and method of administration

Posology

Zyclara (per application: up to 2 sachets, 250 mg imiquimod cream per sachet) should be applied once daily before bedtime to the skin of the affected treatment field (area) for two treatment cycles of 2 weeks each separated by a 2-week no-treatment cycle or as directed by the physician.

The treatment area is the full face or balding scalp.

Local skin reactions in the treatment area are in part anticipated and common due to its mode of action (see section 4.4). A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. However, neither 2-week treatment cycle should be extended due to missed doses or rest periods.

A transient increase in actinic keratosis counts may be observed during treatment due to the likely effect of imiquimod to reveal and treat subclinical lesions. Response to treatment cannot be adequately assessed until resolution of local skin reactions. Patients should continue treatment as prescribed. Treatment should be continued for the full treatment course even if all actinic keratosis appear to be gone.

The clinical outcome of therapy has to be determined after regeneration of the treated skin, approximately 8 weeks after the end of treatment and on appropriate intervals thereafter based on clinical judgment. Lesions that do not respond completely to treatment at 8 weeks after the second treatment cycle should be carefully re-evaluated and one additional 2-week treatment of Zyclara may be considered.

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

Actinic keratosis lesions that have cleared after two Zyclara treatment cycles of 2 weeks and subsequently recur can be re-treated with one or two further Zyclara treatment cycles of 2 weeks following an at least 12 weeks treatment pause.

Hepatic or renal impairment
Patients with hepatic or renal impairment were not included in clinical trials. These patients should be monitored under the close supervision of an experienced physician.

Paediatric population
The safety and efficacy of imiquimod in actinic keratosis in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration
Zyclara is for external use only. Contact with eyes, lips, and nostrils should be avoided.

The treatment area should not be bandaged or otherwise occluded.

The prescriber should demonstrate the proper application technique to the patient to maximise the benefit of Zyclara therapy.

Zyclara should be applied once daily before bedtime to the skin of the affected treatment field (area) and remain on the skin for approximately 8 hours. During this period, showering and bathing should be avoided. Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly. Zyclara should be applied as a thin film to the entire treatment area and rubbed in until the cream vanishes. Up to 2 sachets of Zyclara may be applied to the treatment area (full face or scalp, but not both) at each daily application. Partially-used sachets should be discarded and not reused. Zyclara should be left on the skin for approximately 8 hours; after this time it is essential that the cream is removed by washing the area and the hands with mild soap and water.

Hands should be washed carefully before and after application of cream.

Missed dose
In case a dose is missed, patients should wait until the forthcoming night to apply Zyclara and then continue with the regular schedule. The cream should not be applied more than once daily. Each treatment cycle should not be extended beyond 2 weeks due to missed doses or rest periods.

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

General instructions for treatment

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

Contact with eyes, lips and nostrils should be avoided as imiquimod 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.

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

Because of concern for heightened sunburn susceptibility, use of sunscreen is encouraged, and patients should minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Zyclara. The skin surface area treated should be protected from solar exposure.

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

Local skin reactions

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

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

Systemic reactions

Flu-like systemic signs and symptoms may accompany, or even precede, intense local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, and chills. An interruption of dosing or dose adjustment should be considered (see section 4.8).

Patients with reduced haematologic reserve should be monitored under the close supervision of an experienced physician (see section 4.8).

Special populations

Patients with cardiac, hepatic or renal impairment were not included in clinical trials. These patients should be monitored under the close supervision of an experienced physician.

Use in immunocompromised patients and/or in patients with autoimmune conditions

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

Re-treatment

Information on re-treating actinic keratosis lesions that have cleared after two Zyclara treatment cycles of 2 weeks and subsequently recur is given in section 4.2 and 5.1.

Excipients

Stearyl alcohol and cetyl alcohol may cause local skin reactions (e.g. contact dermatitis). Benzyl alcohol may cause allergic reactions and mild local irritation.

Methyl parahydroxybenzoate (E 218), and propyl parahydroxybenzoate (E 216) may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. This includes studies with immunosuppressive medicinal products. Interactions with systemic medicinal products would be limited by the minimal percutaneous absorption of imiquimod cream.

Due to its immunostimulating properties, imiquimod cream should be used with caution in patients who are receiving immunosuppressive medicinal products (see section 4.4).

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

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/fetal development, parturition or postnatal development (see section 5.3).
Caution should be exercised when prescribing Zyclara to pregnant women. Zyclara should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding
It is unknown whether imiquimod/metabolites are excreted in human milk.
A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zyclara therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile:
The data described below reflect exposure to Zyclara or vehicle in 319 subjects enrolled in two double-blind studies. Subjects applied up to two sachets of Zyclara 3.75% cream or vehicle daily to the skin of the affected area (either entire face or balding scalp, but not both) for two 2-week treatment cycles separated by a 2-week no-treatment cycle.

In clinical trials most patients (159/160) using Zyclara for the treatment of AK experience local skin reactions (most frequently erythema, scab, and exfoliation/application site dryness) at the application site. However, only 11% (17/160) of patients in clinical trials with Zyclara required rest periods (treatment interruption) due to local adverse reactions. Some systemic adverse reactions, including headache 6% (10/160), fatigue 4% (7/160), were reported by Zyclara treated patients in clinical trials.

Tabulated list of adverse reactions

Data presented in the table below reflects:
- exposure to Zyclara or vehicle in above mentioned studies (frequencies very common to uncommon and at greater frequency after vehicle).
- experience with imiquimod 5% cream

Frequencies are defined as:

Very common (≥ 1/10);
Common (≥ 1/100 to < 1/10);
Uncommon (≥ 1/1,000 to < 1/100);
Rare (≥ 1/10,000 to < 1/1,000);
Very rare (<1/10,000) and not known (cannot be estimated from the available data)

System organ class	Frequency	Adverse reactions
Infections and infestations	Common	Herpes simplex
	Uncommon	Infection
		Pustules
	Frequency not known	Skin infection
Blood and lymphatic system disorders	Common	Lymphadenopathy
	Frequency not known	Haemoglobin decreased
		White blood cell count decreased
		Neutrophil count decreased
		Platelet count decreased
Immune system disorders	Rare	Exacerbation of autoimmune conditions
Metabolism and nutrition disorders	Common	Anorexia
		Blood glucose increased
Psychiatric disorders	Common	Insomnia
	Uncommon	Depression
		Irritability
Nervous system disorders	Common	Headache
		Dizziness
Eye disorders	Uncommon	Conjunctival irritation
		Eyelid oedema
Respiratory, thoracic and mediastinal disorders	Uncommon	Nasal congestion
		Pharyngo laryngeal pain
Hepatobiliary disorders	Frequency not known	Hepatic enzyme increased
Gastrointestinal disorders	Common	Nausea
		Diarrhoea
		Vomiting
	Uncommon	Dry mouth
		Abdominal pain
Skin and subcutaneous tissue disorders	Very common	Erythema
		Scab
		Skin exfoliation
		Skin oedema
		Skin ulcer
		Skin hypopigmentation
	Common	Dermatitis
	Uncommon	Face oedema
	Rare	Remote site dermatologic reaction
	Frequency not known	Alopecia
		Erythema multiforme
		Stevens Johnson syndrome
		Cutaneous lupus erythematosus

		Skin hyperpigmentation
Musculoskeletal and connective tissue disorders	Common	Myalgia
		Arthralgia
	Uncommon	Back pain
		Pain in extremity
General disorders and administration site conditions	Very common	Application site erythema
		Application site scabbing
		Application site exfoliation
		Application site dryness
		Application site oedema
		Application site ulcer
		Application site discharge
	Common	Application site reaction
		Application site pruritus
		Application site pain
		Application site swelling
		Application site burning
		Application site irritation
		Application site rash
		Fatigue
		Pyrexia
		Influenza-like illness
		Pain
		Chest pain
	Uncommon	Application site dermatitis
		Application site bleeding
		Application site papules
		Application site paraesthesia
		Application site hyperaesthesia
		Application site inflammation
		Application site scar
		Application site skin breakdown
		Application site vesicles
		Application site warmth
		Asthenia
		Chills
		Lethargy
		Discomfort
		Inflammation

Description of selected adverse reactions

Blood system disorders
Reductions in haemoglobin, white blood cell count, absolute neutrophils and platelets have been observed in clinical trials investigating the use of imiquimod 5% cream. 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.

Skin infections
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.

Hypopigmentation and hyperpigmentation
Reports have been received of localised hypopigmentation and hyperpigmentation following imiquimod 5 % cream use. Follow-up information suggests that these skin colour changes may be permanent in some patients.

Remote site dermatologic reactions
Rare cases of remote site dermatologic reactions, including erythema multiforme, have been reported from clinical trials with imiquimod 5% cream therapy.

Alopecia
Clinical studies investigating the use of imiquimod 5% cream for the treatment of actinic keratosis have detected a 0.4% (5/1214) frequency of alopecia at the treatment site or surrounding area.

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 overdose with imiquimod cream is unlikely due to minimal percutaneous absorption. Studies in rabbits reveal a dermal lethal imiquimod dose of greater than 5 g/kg. Persistent topical overdosing of imiquimod cream could result in severe local skin reactions and may increase the risk for systemic 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 more than 21 sachets of Zyclara. The most clinically serious adverse event reported following multiple oral doses of ≥ 200 mg was hypotension which resolved following oral or intravenous fluid administration.

Management of overdose should consist of treatment of clinical symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotics and chemotherapeutics for dermatological use, antivirals, ATC Code: D06BB10

Pharmacodynamic effects
Imiquimod is an immune response modifier. It is the lead compound of the imidazoline family. Saturable binding studies suggest membrane receptors for imiquimod exists on responding cells; these are called toll-like receptor 7 and 8. Imiquimod induces the release of interferon alpha (IFN-α) and other cytokines from a variety of human and animal cells (e.g. from human monocytes/macrophages and keratinocytes). Topical *in vivo* application of imiquimod cream on mouse skin resulted in increased concentrations of IFN and tumour necrosis factor (TNF) compared with skin of untreated mice. The panel of induced cytokines varies with the cell's tissue origin. In addition, release of cytokines was induced following dermal application and oral administration of imiquimod in various laboratory animals and in human studies. In animal models imiquimod is effective against viral infections and acts as an antitumour agent principally by inducing release of alpha interferon and other cytokines.

Increases in systemic levels of alpha interferon and other cytokines following topical application of imiquimod were also observed in human data.

Clinical efficacy and safety

The efficacy of Zyclara was studied in two double-blind, randomized, vehicle-controlled clinical studies. Patients had 5-20 typical visible or palpable AK lesions in an area that exceeded 25 cm^2 on either the face or balding scalp. 319 subjects with AK were treated with up to 2 sachets once daily of imiquimod 3.75% cream, or a matching vehicle cream for two treatment cycles of 2 weeks separated by a 2-week no-treatment cycle. For the combined trials the complete clearance rate of the full face or balding scalp under imiquimod 3.75% cream was 35.6% (57/160 patients, CI 28.2%, 43.6 %) under vehicle 6.3% (10/159 patients, CI 3.1%, 11.3%) at the 8-week post-treatment visit. No overall differences in safety or effectiveness were observed between patients 65 years or older and the younger patients. Squamous cell carcinoma (SCC) was reported in 1.3% (2/160) of patients treated with imiquimod 3.75%, in 0.6% (1/159) treated with vehicle. This difference was not statistically significant.

In a follow-up study where initially cleared patients with imiquimod 3.75% were followed for at least 14 months without any further AK-treatment, 40.5% of the patients showed sustained complete clearance of the whole treatment area (either full face or scalp) There are no data for imiquimod 3.75% on long-term clearance beyond that.

Two open-label randomized, controlled studies investigated the long-term effects of imiquimod 5% (and not with this 3.75% product) in comparison to topical diclofenac (3% gel). In these studies, the treated AK field was located on the balding scalp or face with a contiguous area of about 40 cm^2 and presenting with a median number of 7 clinically typical AK lesions at baseline. Study treatments were given as officially recommended. These studies showed that imiquimod was better than topical diclofenac in preventing the histological progression of AK lesions to in-situ or invasive squamous cell carcinoma (SCC). In addition, these studies supported the use of up to two additional treatment cycles of imiquimod when the AK lesions are not completely cleared or if the AK lesions recurred after successful initial treatment with imiquimod.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Zyclara in all subsets of the paediatric population in actinic keratosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Less than 0.9% of a topically applied single dose of radiolabelled imiquimod was absorbed through the skin of human subjects.
Systemic exposure (percutaneous penetration) was calculated from recovery of carbon-14 from [^{14}C] imiquimod in urine and faeces.
During a pharmacokinetic study with imiquimod 3.75% cream following application of 2 sachets once daily (18.75 mg imiquimod/day) for up to three weeks to the entire face and/or scalp (approximately 200 cm^2), low systemic absorption of imiquimod was observed in patients with AK. Steady-state levels were achieved in 2 weeks and time to maximal concentrations (Tmax) ranged between 6 and 9 hours after last application.

Distribution
The mean peak serum imiquimod concentration at the end of the pharmacokinetic study was 0.323 ng/mL.

Biotransformation
Orally administered imiquimod is rapidly and extensively metabolised into two main metabolites.

Elimination
The small amount of medicinal product 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.

The apparent half-life following topical dosing of 3.75% imiquimod cream in the pharmacokinetic study was calculated as approximately 29 hours.

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 18-month mouse carcinogenicity study by dermal administration on three days a week did not induce tumours at the application site. Only in female mice, the incidences of hepatocellular adenomas were slightly greater than those for controls. The incidence corresponds well with the spectrum of spontaneous tumours, as is known in mice in correspondence with their age. Therefore, these findings are considered to be incidental. 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. 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 parahydroxybenzoate (E 218)
Propyl parahydroxybenzoate (E 216)
Xanthan gum
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

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 14, 28, and 56 single-use polyester/ white low density polyethylene/ 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/1/12/783/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23/08/2012
Date of latest renewal: 22/03/2017

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.europe.eu.

ANNEX II

A. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Swiss Caps GmbH
Grassingerstraße 9
83043 Bad Aibling
Germany

MEDA Pharma GmbH & Co. KG
Benzstraße 1
61352 Bad Homburg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zyclara 3.75% cream
imiquimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 9.375 mg of imiquimod in 250 mg cream (3.75%).
Each gram of cream contains 37.5 mg of imiquimod.

3. LIST OF EXCIPIENTS

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

Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Cream
14 sachets
28 sachets
56 sachets

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
170 73 Solna
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/783/001 14 sachets
EU/1/12/783/002 28 sachets
EU/1/12/783/003 56 sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zyclara

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET TEXT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Zyclara 3.75% 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

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zyclara 3.75% 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, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their sign of illness are the same as yours.
- If you 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 Zyclara is and what it is used for

Zyclara 3.75% cream contains the active substance imiquimod, which is an Immune Response Modifier (to stimulate the human immune system).

This medicine is prescribed for the treatment of actinic keratosis in adults.

This medicine stimulates your body's own immune system to produce natural substances which help fight your actinic keratosis.

Actinic keratosis appears as rough areas of skin found in people who have been exposed to a lot of sunshine over the course of their lifetime. These areas can be the same colour as your skin or are greyish, pink, red or brown. They can be flat and scaly, or raised, rough, hard and warty.

This medicine should only be used for actinic keratosis on the face or scalp if your doctor has decided that it is the most appropriate treatment for you.

2. What you need to know before you use Zyclara

Do not use Zyclara

- 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 Zyclara:
- if you have previously used this medicine or other similar preparations in a different concentration.
- if you suffer from autoimmune disorders
- if you have had an organ transplant
- if you have an abnormal blood count.

General instructions during treatment

- If you have recently had surgery or medicinal treatment, wait until the area to be treated has healed before using this medicine.
- Avoid contact with the eyes, lips and nostrils. In the event of accidental contact, remove cream by rinsing with water.
- Only use the cream externally (on the skin of face or scalp).
- 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 this medicine.
- If the treated site becomes too uncomfortable, wash the cream off with mild soap and water. Once the discomfort stops you can resume your treatment schedule as recommended. The cream should not be applied more than once daily.
- Do not use sunlamps or tanning-beds, and avoid exposure to sunlight as much as possible during treatment with this medicine. If you go outside during the day use sunscreen and wear protective clothing and a wide-brimmed hat.

Local skin reactions

While using Zyclara, you may experience local skin reactions because of the way it acts on your skin. These reactions can be a sign that the medicine is working as intended.

Whilst using Zyclara and until healed, the treatment area is likely to appear noticeably different from normal skin. There is also a possibility that existing inflammation may temporarily worsen.
This medicine may also cause flu-like symptoms (including tiredness, nausea, fever, muscle and joint pain, and shivering) before or during the occurrence of local skin reactions.
If flu-like symptoms or feeling discomfort or intense local skin reactions occur, a rest period of several days may be taken. You could resume treatment with imiquimod cream after the skin reaction has moderated. However, neither 2-week treatment cycle should be extended due to missed doses or rest periods.
The intensity of the local skin reactions tend to be lower in the second cycle than in the first treatment cycle with Zyclara.

Response to treatment cannot be adequately assessed until resolution of local skin reactions. You should continue treatment as prescribed.
This medicine may reveal and treat actinic keratosis that have not be seen or felt before, and these may later go away. You should continue application for the full treatment course even if all actinic keratosis appear to be gone.

Children and adolescents

This medicine should not be given to children below the age of 18 years because the safety and efficacy in patients below the age of 18 years have not been established. There are no data available of the use of imiquimod in children and adolescents.

Other medicines and Zyclara

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you receive immunosuppressive medicinal products which inhibit the immune system, tell your doctor before starting the treatment.
Avoid the concomitant use of Zyclara and any other imiquimod cream in the same treatment area.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Your doctor will discuss the risks and benefits of using Zyclara during pregnancy. Studies in animals do not indicate direct or indirect harmful effects in pregnancy.

It is not known whether imiquimod passes into breast milk. You should not use Zyclara if you are breast-feeding or plan to breast-feed. Your doctor will discuss if you should discontinue breast-feeding or discontinue Zyclara treatment.

Driving and using machines

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

Zyclara contains methyl parahydroxybenzoate, propyl parahydroxybenzoate, cetyl alcohol, stearyl alcohol and benzyl alcohol

Methyl parahydroxybenzoate (E 218), and propyl parahydroxybenzoate (E 216), may cause allergic reactions (possibly delayed). Cetyl alcohol and stearyl alcohol may cause local skin reactions (e.g. contact dermatitis).
This medicine contains 5 mg benzyl alcohol in each sachet. Benzyl alcohol may cause allergic reactions and mild local irritation.

3. How to use Zyclara

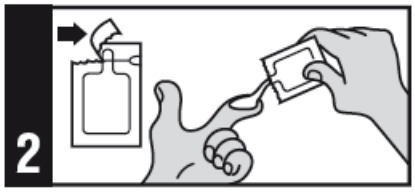
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Do not use this medicine until your doctor has shown you the right way to use it.

This medicine should only be used for actinic keratosis on the face and scalp.

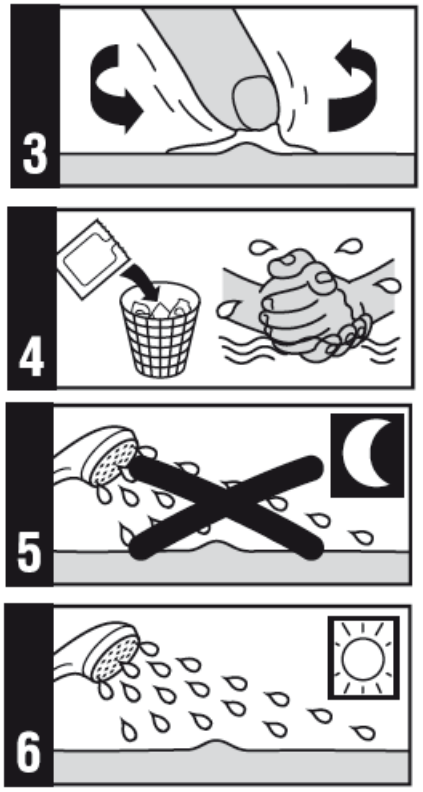
Dosage
Apply this medicine to the affected area once a day just before bedtime.
Maximum daily dose is 2 sachets (500 mg = 2 sachets of 250 mg each).
This medicine should not be applied to areas larger than either the full face or balding scalp.

Method of administration

1. Before going to bed, wash your hands and the treatment area carefully with mild soap and water. Dry hands thoroughly and allow the area to dry.



2. Open a new sachet of Zyclara just before use and squeeze some cream onto your fingertip. No more than 2 sachets should be used per application.



3. Apply a thin layer of Zyclara to the affected area. Rub gently into the area until the cream vanishes. Avoid contact with the eyes, lips and nostrils.

4. After application of the cream, throw away the opened sachet. Wash hands well with soap and water.

5. Leave Zyclara on the skin for about 8 hours. Do not shower or bathe the area during this time. Do not cover the treated area with bandages or other dressings.

6. After about 8 hours, wash the area where Zyclara was applied with mild soap and water.

Duration of treatment
The treatment starts with a daily application for two weeks, followed by a break without any application for two weeks, and then ends with a daily application again for two weeks.

If you use more Zyclara than you should

If you have applied too much cream, wash the extra away with mild soap and water.
When any skin reaction has gone you may then continue with your treatment in the recommended regular schedule. The cream should not be applied more than once daily.

If you accidentally swallow this medicine please contact your doctor immediately.

If you forget to use Zyclara

If you miss a dose of Zyclara, wait until the next night to apply it and then continue with the regular schedule. The cream should not be applied more than once daily. Each treatment cycle should last no longer than two weeks, even if you have missed doses.

If you stop using Zyclara

Talk to your doctor before you stop treatment with Zyclara.

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

4. Possible side effects

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

Seek medical attention right away if any of these severe side effects occur when using this medicine:

Serious skin reactions (frequency not known) with 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. If you experience these, stop using this medicine and tell your doctor immediately.

In some individuals a lowering of blood counts was noted (frequency not known). This might make you more susceptible to infections, make you bruise more easily or cause tiredness. If you notice any of these symptoms, tell your doctor.
Some patients who suffer from autoimmune disorders may experience worsening of their condition. If you notice any change during treatment with Zyclara, tell your doctor.
If there is pus or another sign of skin infection (frequency not known), discuss this with your doctor.

Many of the side effects of this medicine are due to its local action on your skin. Local skin reactions can be a sign that the medicine is working as intended. If your skin reacts badly or becomes too uncomfortable when using this medicine, stop applying the cream and wash the area with mild soap and water. Then contact your doctor or pharmacist. He may advise you to stop applying this medicine for a few days (i.e. to have a short rest from treatment).

The following side effects with imiquimod were reported:

Very common (may affect more than 1 in 10 people)
- Skin redness, scabbing, skin scaling, discharge, skin dryness, skin swelling, skin ulcer, and reduced skin pigmentation at the application site

Common (may affect up to 1 in 10 people)
- Further reactions at the application site e.g. skin inflammation, itching, pain, burning, irritation, and rash
- Swollen glands
- Headache
- Dizziness
- Loss of appetite
- Nausea
- Diarrhoea
- Vomiting
- Flu-like symptoms
- Fever
- Pain
- Muscle and joint pain
- Chest pain
- Insomnia
- Tiredness
- Viral infection (herpes simplex)
- Increase in blood glucose

Uncommon (may affect up to 1 in 100 people)
- Changes at the application site, e.g. bleeding, small swollen areas in the skin, inflammation, pins and needles, increased sensitivity to touch, scarring, feeling of warmth, skin breakdown, blisters or pustules
- Weakness
- Shivering
- Lack of energy (lethargy)
- Discomfort
- Swelling of the face
- Back pain
- Pain in limbs
- Stuffy nose

- Throat pain
- Eye irritation
- Swelling of the eyelid
- Depression
- Irritability
- Dry mouth
- Abdominal pain

Rare (may affect up to 1 in 1,000 people)
- Flaring up of autoimmune conditions (a disease that results from an abnormal immune response is an autoimmune disease)
- Skin reactions remote from the application site

Frequency not known (frequency cannot be estimated from the available data)
- Changes in skin colour
  Some patients have experienced changes in skin colour in the area where Zyclara was applied. While these changes have tended to improve with time, in some patients they may be permanent.
- Hair loss
  A small number of patients have experienced hair loss at the treatment site or surrounding area.
- Increase in liver enzymes
  There have been reports of increased liver enzymes.

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 Zyclara

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

Do not use this medicine after the expiry date which is stated on the outer carton and the label after EXP.
The expiry date refers to the last day of that month.
Do not store above 25 °C.

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 Zyclara contains
- The active substance is imiquimod. Each sachet contains 9.375 mg of imiquimod in 250 mg cream (100 mg of cream contains 3.75 mg imiquimod).
- The other ingredients are isostearic acid, benzyl alcohol, cetyl alcohol, stearyl alcohol, white soft paraffin, polysorbate 60, sorbitan stearate, glycerol, methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), xanthan gum, purified water (see also section 2 “Zyclara contains methyl parahydroxybenzoate, propyl parahydroxybenzoate, cetyl alcohol, stearyl alcohol and benzyl alcohol”).

What Zyclara looks like and contents of the pack

- Each Zyclara 3.75% cream sachet contains 250 mg of a white to slightly yellow cream with a uniform appearance.
- Each box contains 14, 28 or 56 single-use polyester/ white low density polyethylene/aluminium foil sachets. Not all pack sizes may be marketed.

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