PRODUCT MONOGRAPH

PrZYCLARA®
Imiquimod Cream
2.5% and 3.75%

Immune response modifier

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Date of Revision:
October 29, 2020

Submission Control No: 241058

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All non-medicinal ingredients
Topical	Cream (2.5 and 3.75% w/w), Available in pumps containing 7.5 g of cream	Isostearic Acid, Cetyl Alcohol, Stearyl Alcohol, White Petrolatum, Polysorbate 60, Sorbitan Monostearate, Glycerin, Xanthan Gum, Purified Water, Benzyl Alcohol, Methylparaben and Propylparaben

INDICATIONS AND CLINICAL USE

ZYCLARA Cream is indicated for:

- the topical field (area) treatment of multiple clinically typical visible or palpable actinic keratoses (AK), whether presenting at the start of therapy or revealed during therapy, of the face or balding scalp in immunocompetent adults.

Geriatrics (> 65 years of age)
No overall differences in safety or effectiveness were observed in clinical studies between the geriatric population and younger subjects (see WARNINGS AND PRECAUTIONS, Geriatrics).

Pediatrics
Safety and efficacy in patients below the age of 18 years have not been established (see WARNINGS AND PRECAUTIONS, Pediatrics).

Immunosuppressed
The safety and efficacy of ZYCLARA Cream in immunosuppressed patients have not been established (see WARNINGS AND PRECAUTIONS, Immune).

CONTRAINDICATIONS

ZYCLARA Cream is contraindicated in individuals with a history of sensitivity reactions to imiquimod or to any of the components in the formulation. It should be discontinued if

hypersensitivity to any of its ingredients is noted (see WARNINGS AND PRECAUTIONS, Sensitivity).

WARNINGS AND PRECAUTIONS

General

The efficacy of ZYCLARA Cream in the prevention of squamous cell carcinoma (SCC) associated with AK has not been established.

The safety and efficacy of ZYCLARA Cream topically applied to an area larger than the face or balding scalp (approximately 200 cm^2) has not been established. Therefore, topical application of ZYCLARA Cream to larger areas is not recommended.

Systemic Reactions

Flu-like signs and symptoms may accompany, or even precede, local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, and chills. An interruption of dosing or dose adjustment and an assessment of the patient should be considered (see ADVERSE REACTIONS).

Lymphadenopathy occurred in 1.9% of subjects with actinic keratosis treated with ZYCLARA Cream, 3.75% and in 2.5% of subjects treated with ZYCLARA Cream, 2.5% (see ADVERSE REACTIONS). This reaction resolved in all subjects by 4 weeks after completion of treatment.

Carcinogenesis and Mutagenesis

In a hairless mouse photocarcinogenicity study with solar ultraviolet light irradiation, imiquimod cream enhanced UVR-induced skin tumour development, but not beyond that of the vehicle cream. Vehicle cream alone enhanced ultraviolet induced skin tumour development (see TOXICOLOGY, Carcinogenicity). It is recommended that patients minimize or avoid natural or artificial sunlight exposure during treatment with ZYCLARA.

Immune

The safety and efficacy of ZYCLARA Cream in immunosuppressed patients have not been established.

ZYCLARA topical cream should be used with caution in patients with pre-existing autoimmune conditions (including thyroiditis, multiple sclerosis, spondyloarthropathy, psoriasis, ulcerative colitis) (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Sensitivity

Hypersensitivity reactions (urticaria) and erythema multiforme have been reported in patients receiving imiquimod cream, however causality has not been established. ZYCLARA Cream should be discontinued immediately if these events occur.

Skin

Local skin reactions such as erythema, scabbing/crusting, flaking/scaling/dryness, and edema are common.

Intense local skin reactions including erythema, scabbing/crusting and erosion/ulceration can occur after a few applications of ZYCLARA Cream and may require an interruption of dosing (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

ZYCLARA Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

Should a severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water and drying the area thoroughly. Treatment with ZYCLARA Cream can be resumed after consultation with the treating physician, and once the skin reaction has subsided.

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of ZYCLARA Cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (e.g. hat) when using ZYCLARA Cream. Patients with sunburn should be advised not to use ZYCLARA Cream until fully recovered. Patients who may have considerable sun exposure, e.g., due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using ZYCLARA Cream. Phototoxicity has not been adequately assessed for ZYCLARA Cream. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Imiquimod cream shortened the time to skin tumour formation in an animal photoco-carcinogenicity study (see TOXICOLOGY, Carcinogenicity). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

Special Populations

Pregnant Women

Imiquimod was not teratogenic in rat or rabbit teratology studies. In rats at a high maternally toxic dose (28 times human dose on a mg/m^2 basis), reduced pup weights and delayed ossification were observed. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

It is not known whether topically applied imiquimod is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYCLARA Cream is administered to nursing women.

Pediatrics (< 18 years of age)

Safety and efficacy in patients below the age of 18 years have not been established.

Geriatrics (> 65 years of age)
Of the 160 subjects treated with ZYCLARA Cream, 2.5% in the clinical studies, 72 subjects were 65 years or older. Of the 160 subjects treated with ZYCLARA Cream, 3.75% in the clinical studies, 78 subjects were 65 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No other clinical experience has identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions
There have been three pivotal phase 3 studies supporting the use of ZYCLARA Cream for the treatment of actinic keratosis. The results of Studies 1 and 2 are pooled, while the data for Study 3 is presented separately.

Clinical Trial Experience from Studies 1 and 2
The data described below reflect exposure to ZYCLARA Cream 2.5%, 3.75% or placebo in 479 subjects enrolled in two double-blind, placebo-controlled studies. Subjects in these trials were not to have had cryosurgical procedures in the treatment area within 90 days prior to treatment. Subjects applied ZYCLARA Cream or placebo daily to the skin of the affected area (either the entire face or balding scalp) for two 2-week treatment cycles separated by a 2-week no treatment period.

Table 1: Adverse Reactions Occurring in > 1% of Subjects treated with ZYCLARA Cream, 2.5% or 3.75%, and at a Greater Frequency than with Placebo in the Combined Studies

Preferred Term	ZYCLARA Cream, 2.5% (N=160)	ZYCLARA Cream, 3.75% (N=160)	Placebo (N=159)
Headache	3 (1.9%)	10 (6.3%)	5 (3.1%)
Application site pruritus	6 (3.8%)	7 (4.4%)	1 (0.6%)
Fatigue	2 (1.3%)	7 (4.4%)	0 (0%)
Influenza like illness	6 (3.8%)	1 (0.6%)	0 (0%)
Nausea	1 (0.6%)	6 (3.8%)	2 (1.3%)
Application site irritation	4 (2.5%)	5 (3.1%)	0 (0%)
Application site pain	2 (1.3%)	5 (3.1%)	0 (0%)
Pyrexia	0 (0%)	5 (3.1%)	0 (0%)
Anorexia	0 (0%)	4 (2.5%)	0 (0%)
Arthralgia	4 (2.5%)	2 (1.3%)	0 (0%)
Dizziness	1 (0.6%)	4 (2.5%)	0 (0%)
Herpes simplex	0 (0%)	4 (2.5%)	1 (0.6%)
Lymphadenopathy	4 (2.5%)	3 (1.9%)	0 (0%)
Oral herpes	4 (2.5%)	0 (0%)	0 (0%)

Pain	1 (0.6%)	4 (2.5%)	0 (0%)
Bronchitis	3 (1.9%)	1 (0.6%)	0 (0%)
Cheilitis	3 (1.9%)	0 (0%)	0 (0%)
Chest pain	0 (0%)	3 (1.9%)	0 (0%)
Diarrhea	2 (1.3%)	3 (1.9%)	0 (0%)
Pneumonia	3 (1.9%)	0 (0%)	1 (0.6%)
Angina pectoris	2 (1.3%)	0 (0%)	0 (0%)
Aphthous stomatitis	2 (1.3%)	1 (0.6%)	0 (0%)
Application site swelling	0 (0%)	2 (1.3%)	0 (0%)
Blood glucose increased	0 (0%)	2 (1.3%)	0 (0%)
Dermatitis	0 (0%)	2 (1.3%)	0 (0%)
Food poisoning	0 (0%)	2 (1.3%)	0 (0%)
Insomnia	0 (0%)	2 (1.3%)	0 (0%)
Pharyngolaryngeal pain	2 (1.3%)	0 (0%)	1 (0.6%)
Procedural pain	2 (1.3%)	0 (0%)	1 (0.6%)
Rhinitis	2 (1.3%)	0 (0%)	0 (0%)
Seborrheic keratosis	0 (0%)	2 (1.3%)	0 (0%)
Squamous cell carcinoma	0 (0%)	2 (1.3%)	1 (0.6%)
Vomiting	0 (0%)	2 (1.3%)	1 (0.6%)

Table 2: Application Site Reactions in Subjects treated with ZYCLARA Cream, 2.5% or 3.75%, as Assessed by the Investigator

Included Term	ZYCLARA Cream, 2.5% (N=160)	ZYCLARA Cream, 3.75% (N=160)	Placebo (N=159)
Any application site reaction	10 (6.3%)	17 (10.6%)	2 (1.3%)
Application site pruritus	6 (3.8%)	7 (4.4%)	1 (0.6%)
Application site irritation	4 (2.5%)	5 (3.1%)	0 (0%)
Application site pain	2 (1.3%)	5 (3.1%)	0 (0%)
Application site swelling	0 (0%)	2 (1.3%)	0 (0%)
Application site dryness	1 (0.6%)	0 (0%)	0(0%)
Application site infection	1 (0.6%)	0 (0%)	0 (0%)
Application site paraesthesia	0 (0%)	1 (0.6%)	1 (0.6%)
Application site scar	0 (0%)	1 (0.6%)	0(0%)

Local skin reactions were collected independently of the adverse event "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen.

The most frequently reported local skin reactions were erythema, flaking/scaling/dryness, and scabbing/crusting. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Table 3: Local Skin Reactions in the Treatment Area in Subjects treated with ZYCLARA Cream, 2.5% or 3.75%, as Assessed by the Investigator

	ZYCLARA Cream, 2.5% (N=160)		**ZYCLARA Cream, 3.75% (N=160)**		**Placebo (N=159)**	
	All Grades	Severe	All Grades	Severe	All Grades	Severe
Erythema	154 (96.3%)	23 (14.4%)	154 (96.3%)	40 (25.2%)	124 (78.0%)	0 (0.0%)
Edema	101 (63.1%)	6 (3.8%)	120 (75.0%)	9 (5.7%)	31 (19.5%)	0 (0.0%)
Weeping/Exudate	63 (39.4%)	2 (1.3%)	81 (50.6%)	9 (5.7%)	6 (3.8%)	0 (0.0%)
Flaking/Scaling/Dryness	141 (88.1%)	7 (4.4%)	147 (91.9%)	13 (8.2%)	123 (77.4%)	2 (1.3%)
Scabbing/Crusting	135 (84.4%)	15 (9.4%)	149 (93.1%)	22 (13.8%)	72 (45.3%)	0 (0.0%)
Erosion/Ulceration	84 (52.5%)	15 (9.4%)	99 (61.9%)	17 (10.7%)	14 (8.8%)	0 (0.0%)

Local skin reactions may extend beyond treatment area.

Overall, in the clinical trials, 11% (17/160) subjects in the ZYCLARA Cream 2.5% arm, and 0% In the vehicle cream arm required rest periods due to adverse local skin reactions.

Clinical Trial Experience from Study 3

The data described below reflect exposure to ZYCLARA Cream, 3.75% or vehicle following cryosurgery in 247 subjects with multiple facial AKs enrolled in a double-blind, vehicle-controlled trial. Study cream treatment was initiated after facial skin was sufficiently healed from cryosurgery (mean 12 days, range 5-25 days). Subjects applied up to two packets of ZYCLARA Cream or vehicle daily for two 2-week treatment cycles separated by a 2-week no treatment period.

Table 4: Adverse Events Occurring in > 1% of Subjects Treated with ZYCLARA Cream, 3.75% Following Cryosurgery and at a Greater Frequency than with Vehicle

Preferred Term	**ZYCLARA Cream 3.75% following cryosurgery (N=126)**	**Vehicle following cryosurgery (N=121)**
Application site pruritus	12 (9.5)	1 (0.8)
Application site irritation	7 (5.6)	1 (0.8)
Application site pain	6 (4.8)	0 (0.0)
Myalgia	6 (4.8)	1 (0.8)

Nausea	6 (4.8)	0 (0.0)
Fatigue	5 (4.0)	1 (0.8)
Headache	3 (2.4)	0 (0.0)
Influenza-like illness	3 (2.4)	1 (0.8)
Procedural pain	3 (2.4)	0 (0.0)
Anorexia	2 (1.6)	0 (0.0)
Conjunctivitis	2 (1.6)	0 (0.0)
Dizziness	2 (1.6)	0 (0.0)
Hemorrhage	2 (1.6)	0 (0.0)
Lymphadenopathy	2 (1.6)	0 (0.0)
Oedema peripheral	2 (1.6)	0 (0.0)
Pain in extremity	2 (1.6)	0 (0.0)
Paraesthesia	2 (1.6)	0 (0.0)
Staphylococcal infection	2 (1.6)	0 (0.0)

Table 5: Local Skin Reactions in the Treatment Area in Subjects Treated with ZYCLARA Cream, 3.75% Following Cryosurgery as Assessed by the Investigator

	ZYCLARA Cream 3.75% following cryosurgery (N=126)		**Vehicle following cryosurgery (N=121)**	
	All Grades*	Severe	All Grades*	Severe
Erythema	125 (99.2)	36 (28.6)	88 (72.7)	2 (1.7)
Scabbing/Crusting	112 (88.9)	16 (12.7)	22 (18.2)	0 (0.0)
Flaking/Scaling/Dryness	114 (90.5)	9 (7.1)	81 (66.9)	0 (0.0)
Edema	93 (73.8)	2 (1.6)	9 (7.4)	0 (0.0)
Erosion/Ulceration	60 (47.6)	2 (1.6)	1 (0.8)	0 (0.0)
Weeping/Exudate	64 (50.8)	4 (3.2)	3 (2.5)	0 (0.0)

* All Grades: mild, moderate or severe

Local skin reactions may extend beyond treatment area.

Other adverse reactions observed in subjects treated for AK with regimens of 3.75% imiquimod cream or 2.5% imiquimod cream (longer than 2-week cycles) include: application site bleeding, application site discomfort, application site erythema, application site hypersensitivity, blood cholesterol increase, burning sensation, chills, cough, dry skin, diverticulitis, dysgeusia, dysphonia, ear pain, herpes zoster, impetigo, influenza, lethargy, lower respiratory tract infection, musculoskeletal pain, myalgia, nasopharyngitis, pancytopenia, periorbital oedema, pruritus, sinus congestion, sinusitis, tachycardia, stomach discomfort, upper respiratory infection, urinary tract infection, and vertigo.

Post-Market Adverse Drug Reactions

Rare reports have been received of either the onset or exacerbation of autoimmune conditions (including thyroiditis, multiple sclerosis, spondyloarthropathy, psoriasis, ulcerative colitis) in association with imiquimod 5% cream therapy.

The following adverse reactions have been identified during post-approval use of ALDARA (imiquimod) Cream, 5%. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Application Site Disorders: tingling at the application site.

Body as a Whole: angioedema.

Cardiovascular: capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, supraventricular tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope.

Endocrine: thyroiditis.

Gastro-Intestinal System Disorders: abdominal pain.

Hematological: decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma.

Hepatic: abnormal liver function.

Infections and Infestations: herpes simplex.

Musculo-Skeletal System Disorders: arthralgia.

Neuropsychiatric: agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide.

Respiratory: dyspnea.

Urinary System Disorders: proteinuria, urinary retention, dysuria.

Skin and Appendages: exfoliative dermatitis, erythema multiforme, hyperpigmentation, hypertrophic scar.

Vascular: Henoch-Schoenlein purpura syndrome.

DRUG INTERACTIONS

Overview

Interactions between ZYCLARA Cream with other drugs have not been established.
As an immune response modifier, imiquimod is not recommended for use concurrently with immunosuppressive drugs such as tacrolimus, pimecrolimus, mycophenolate mofetil, cyclosporine or methotrexate.

Concomitant use of corticosteroids with imiquimod may potentially limit efficacy.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

ZYCLARA Cream (2 full actuations of the pump) 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 period or as directed by physician.

Treatment with ZYCLARA Cream should not be initiated until the skin has healed from cryosurgery, which, if performed, should be completed at least 2 weeks prior to ZYCLARA Cream application.

Patients should be prescribed no more than two 7.5 g pumps for the total 2-cycle treatment course.

Missed Dose

Each treatment cycle should not be extended beyond 2 weeks due to missed doses or rest periods.

Administration

Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly. ZYCLARA Cream should be applied as a thin film to the entire treatment area and rubbed in until the cream is no longer visible. Up to 2 full actuations of the pump of ZYCLARA Cream may be applied to the treatment area (face or scalp, but not both) at each daily application. When the treatment course is complete, any remaining pumps should be discarded. **ZYCLARA Cream should be left on the skin for approximately 8 hours, after which time the cream should be removed by washing the area and the hands with mild soap and water.** The prescriber should demonstrate the proper application technique to maximize the benefit of ZYCLARA Cream therapy.

Use of the cream in or near the eyes, lips and nostrils should be avoided. The application site is not to be occluded.

Local skin reactions in the treatment area are common (see ADVERSE REACTIONS). A rest period of several days and interruption of dosing may be considered if required by the patient's discomfort or severity of the local skin reaction. **However, each treatment cycle should not be extended beyond 2 weeks due to missed doses or rest periods.** Response to treatment cannot be adequately assessed until resolution of local skin reactions. Lesions that do not respond to treatment should be carefully re-evaluated and management reconsidered.

A transient increase in AK lesion counts may be observed during treatment due to the likely effect of imiquimod on subclinical lesions. The patient should continue dosing as prescribed.

OVERDOSAGE

Overdosage of ZYCLARA Cream in humans is unlikely due to minimal percutaneous absorption. Animal studies reveal a rabbit dermal lethal imiquimod dose of greater than 5000 mg/kg. Persistent topical overdosing of ZYCLARA Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions.

The most clinically serious adverse event reported following multiple oral imiquimod doses of ≥ 200 mg was hypotension which resolved following oral or intravenous fluid administration.

For management of suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

In vitro studies have demonstrated that imiquimod induces the release of interferon alpha (IFN-α) and other cytokines from human monocytes/macrophages and keratinocytes. The panel of cytokines induced varied with the cell's tissue origin. 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.

Pharmacodynamics

The mechanism of action of imiquimod in treating actinic keratosis (AK) lesions is unknown. While the following have been observed, the clinical significance of these observations in AK is not known. In a study of 58 patients with AK treated with imiquimod 3 times per week, the response of biomarkers sensitive to imiquimod after 16 weeks of dosing increased compared to the response after the first dose. For interleukin-1 antagonist, the median concentration observed following multiple dosing was < 2-fold higher than that after single dose administration, for interferon-α was < 3-fold, and for 2'5'-oligoadenylate synthetase was approximately 3-fold.

Pharmacokinetics

Percutaneous absorption of imiquimod has been studied through intact healthy skin, the skin of genital warts, and lesions of sun damaged skin. Percutaneous absorption of [^{14}C] imiquimod was minimal in a study involving six healthy subjects treated with a single topical application (5 mg) of [^{14}C] imiquimod in cream formulation. No radioactivity [^{14}C] was detected in the serum (lower limit of quantitation is 1 ng/mL) and < 0.9% of the radiolabelled dose was excreted in the urine and feces following topical application.

ZYCLARA Cream, 3.75% exhibited low systemic exposure to imiquimod and its metabolites when it was applied daily for 3 weeks (18.75 mg) to the entire face and/or balding scalp (approximately 200 cm^2) of patients with AK (N=17). A mean (median) peak serum drug

concentration at the end of week 3 was approximately 0.323 ng/mL. Steady-state levels were achieved in 2 weeks and T_{max} ranged between 6 and 9 hours.

The apparent half-life following topical dosing of 3.75% imiquimod cream was calculated as 29 hours after daily administration of 18.75 mg for 3 weeks.

Special Populations and Conditions

Age
No formal pharmacokinetic study was conducted to examine age related differences in the pharmacokinetic profile of ZYCLARA Cream.

Gender
During 3 weeks of treatment, the C_{max} and AUC_{0-24} on Day 21 appeared to be similar in female and male subjects and lower in male subjects who applied ZYCLARA Cream, 3.75% to the balding scalp rather than the face.

STORAGE AND STABILITY

Store between 15°C and 25°C. Avoid freezing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ZYCLARA Cream, 2.5% and 3.75% are supplied as follows:

- Pump which contains 7.5g of the cream.

Each actuation of the pump delivers 235 mg of cream (a similar amount as one packet).

Each gram of ZYCLARA Cream, 2.5% or 3.75% contains 25.0 mg or 37.5 mg of imiquimod, respectively, in an off-white to faintly yellow oil-in-water vanishing cream base consisting of Isostearic Acid, Cetyl Alcohol, Stearyl Alcohol, White Petrolatum, Polysorbate 60, Sorbitan Monostearate, Glycerin, Xanthan Gum, Purified Water, Benzyl Alcohol, Methylparaben, and Propylparaben.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

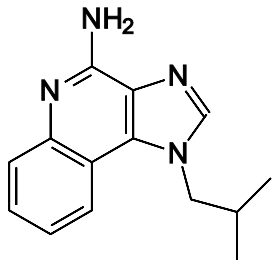
Common name: Imiquimod (USAN, INN)

Chemical name: 1-(2-methylpropyl)-1H-imidazo[4,5-c] quinolin-4-amine

Molecular formula: $C_{14}H_{16}N_4$

Molecular mass: 240.3 g/mol

Structural formula:



Physicochemical properties

Physical Form:	Crystalline solid that varies in colour from white to off-white or buff. The compound has no odour.
Solubility:	Practically insoluble in most common organic solvents and in aqueous systems except at extremely low pH conditions. It can be made soluble to the extent of at least 100 mg/mL in methanol (as a salt) upon the addition of a few drops of hydrochloric or acetic acid. Soluble in fatty acids such as oleic acid and isostearic acid.
pKa Value:	The ionization constant for imiquimod was determined by ultraviolet (UV) spectroscopy and pH-solubility to be about 7.5.
Melting point:	297- 299°C with sublimation.

CLINICAL TRIALS

There have been three pivotal phase 3 studies supporting the use of ZYCLARA Cream for the treatment of actinic keratosis. Subjects enrolled in Studies 1 and 2 were not to have had cryosurgical procedures in the treatment area within 90 days prior to treatment, while subjects in Study 3 initiated study cream treatment after facial skin was sufficiently healed from cryosurgery (mean 12 days). The results of Studies 1 and 2 are pooled, while the data for Study 3 is presented separately.

Clinical Studies 1 and 2

In two double-blind, randomized, placebo-controlled clinical studies, 479 subjects with AK were treated with 2.5% imiquimod cream, 3.75% imiquimod cream, or a matching placebo (vehicle) cream. Studies enrolled subjects >18 years of age with 5-20 typical visible or palpable AK lesions of the face or scalp in an area that exceeded 25cm^2. Study cream was applied to full face or balding scalp once daily for two 2-week treatment cycles separated by a 2-week no-treatment period. Subjects then continued in the study for an 8-week follow-up period during which they returned for clinical observations and safety monitoring. Study subjects ranged from 36 to 90 years of age and 55% had Fitzpatrick skin type I or II. All ZYCLARA Cream-treated subjects were Caucasians.

On a scheduled dosing day, the study cream was applied to the entire treatment area prior to normal sleeping hours and left on for approximately 8 hours. Efficacy was assessed by AK lesion counts at the 8-week post-treatment visit. All AKs in the treatment area were counted, including baseline lesions as well as new or sub-clinical AK lesions which appeared during therapy.

Complete clearance required clearance of all lesions. The partial clearance rate and percent reductions of AKs were measured relative to the numbers of AK lesions at baseline. Partial clearance rate was defined as the proportion of subjects in whom the number of baseline AKs was reduced by 75% or more. Complete and partial clearance rates, and percent reductions in AK counts from baseline are shown in Table 6 below.

Table 6: Efficacy Endpoints for Clinical Studies 1 and 2 (Treatment of Actinic Keratosis with 2.5% and 3.75% Imiquimod Cream)[a]

	ZYCLARA Cream, 2.5%	**ZYCLARA Cream, 3.75%**	**Placebo Cream**
Complete Clearance Rate	30.6% (49/160)	35.6% (57/160)	6.3% (10/159)
p-value vs. Placebo	<0.001	<0.001	
Partial Clearance Rate	48.1% (77/160)	59.4% (95/160)	22.6% (36/159)
p-value vs. Placebo	<0.001	<0.001	
Percent Reduction of AKs (median)	71.8%	81.8%	25.0%
p-value vs. Placebo	<0.001	<0.001	

[a] Studies GW01-0702 and GW01-0704

Sub-clinical AK lesions may become apparent in the treatment area during treatment with ZYCLARA Cream. During the course of treatment, approximately 85% of subjects experienced a transient increase in AK lesions relative to the number present at baseline within the treatment area. Subjects with an increase in AK lesions had a similar response to those with no increase in AK lesions.

Subjects achieving complete clearance of all AKs at End-of-Study in the studies described above were eligible to enroll in an open-label, 12-month observational study. Thirty-nine (39) eligible subjects treated with ZYCLARA Cream, 2.5%, 42 treated with ZYCLARA Cream, 3.75% were followed for up to 12 months to determine the proportion of subjects who sustained clearance of all AKs (new or old) in the previous treatment area. The rate of sustained complete clearance of actinic keratosis one year after completion of the previous study was 33.3% (13/39) for those treated with ZYCLARA Cream, 2.5% and 40.5% (17/42) for those treated with ZYCLARA Cream, 3.75%.

Clinical Study 3
A double-blind, vehicle-controlled, clinical study was conducted in 247 subjects with a minimum of 10 facial AKs following cryosurgery of selected facial AKs. Prior to assignment to treatment arm, all subjects had a minimum of 5 visible lesions not treated with cryosurgery, and 5 to 14 lesions that were treated with cryosurgery. Eligible subjects applied ZYCLARA Cream, 3.75% or vehicle to the entire face, including areas treated and healed from cryosurgery. Up to two packets of study cream were applied daily for two 2-week treatment cycles separated by a 2-week no-treatment period.

Randomized subjects ranged from 39 to 87 years of age; 71% were Fitzpatrick skin type I or II; and all ZYCLARA Cream, 3.75%-treated subjects were Caucasians. At Baseline subjects had a mean of 16 AKs (median 14 and range 10-50); a mean of 6.6 AKs (median 6 and range of 5-14 AKs) were treated with cryosurgery. Subjects were followed to Week 26 (20 weeks after the last dose of study medication). All AKs in the treatment area were counted, including baseline lesions, as well as lesions which appeared during therapy. Complete clearance required absence of any lesions including those that appeared during therapy in the treatment area.

Changes in AK lesion counts from Baseline to Week 26 were measured for all AKs and showed a median percent reduction of 86.5% with imiquimod 3.75% treatment compared with a 50.0% reduction with placebo treatment.

Table 7: Efficacy Endpoints for Clinical Study 3 (Treatment of Actinic Keratosis with 3.75% Imiquimod Cream When Used Within 2 Weeks Following Cryosurgery)

	ZYCLARA Cream	Placebo
Median number of lesions at baseline (median number of lesions treated with cryosurgery)	**14.0 (6.0)**	**14.0 (6.0)**
Median percent change in AK lesion counts from baseline*	-86.5%	-50.0%
Complete clearance rate	30.2% (38/126)	3.3% (4/121)

*All AKs consist of lesions treated with cryosurgery and lesions not treated with cryosurgery

DETAILED PHARMACOLOGY

Pharmacodynamics

Imiquimod is an immune response modifier that is not a nucleoside analogue. Saturable binding studies suggest a membrane receptor for imiquimod exists on responding cells. In vitro studies have demonstrated that imiquimod induces the production of IFN and other cytokines from a variety of human and animal cells. In addition, cytokines were produced following dermal application and oral administration in various laboratory animals and in human studies following oral administration of imiquimod. In animal models imiquimod is an effective antiviral and antitumor agent whose activity is principally due to induction of alpha interferon, but other cytokines are also involved.

In vitro studies using isolated guinea pig myocardium, showed stimulation with tachyphylaxis development after multiple doses. Moderate to marked inhibition of agonist-induced contractions was observed in isolated guinea pig tracheal strips. Intravenous administration of a bolus dose of imiquimod caused CNS and cardiac stimulation in dogs. Little activity was found in inflammatory rat models. Some local anaesthetic activity, slight effect on locomotor, and slight effect on hexobarbital induced sleep time were observed in the mouse.

Pharmacokinetics and Metabolism

Animal and human dermal pharmacokinetic results indicate that minimal, if any, systemic absorption occurs following dermal application of imiquimod cream. Imiquimod was not quantifiable in the serum of rats dosed topically three times per week at 5 mg/kg for 4 weeks; low levels of metabolite were quantifiable after the last, but not after the first dose. In guinea pigs, after a single large (21 mg/kg) topical dose of [^{14}C] imiquimod as a 5% cream, only low concentrations of imiquimod were quantifiable in plasma.

Oral ADME (absorption, distribution, metabolism, elimination) studies in laboratory animals, revealed extensive biotransformation followed by both urinary and biliary excretion of metabolites. Tissue distribution is rapid with clearance after 2 to 3 days with the exception of pigmented tissues - skin and uveal tract of the eye. No evidence of ocular toxicity was found in six-month oral rat and monkey imiquimod toxicity studies conducted at high daily doses.

Percutaneous absorption of 5% imiquimod cream following topical application for 8-12 hours was observed across the intact skin of healthy subjects and the affected skin of subjects with either genital warts or AK. In subjects with AK, urinary recovery less than 0.6% of the applied dose was seen. Because of this low percutaneous absorption, serum levels of imiquimod and metabolites were low or undetectable in these subjects.

TOXICOLOGY

Acute Toxicity

Acute dermal toxicity studies in rabbits with unformulated imiquimod under occlusion did not reveal any toxic effects at very high dose levels - 5000 mg/kg. When administered orally, intraperitoneally, subcutaneously or intravenously, single dose studies revealed that imiquimod produced central nervous system (CNS) stimulation and convulsions at lethal doses. However, signs of CNS toxicity did not occur when animals were given lower repeat doses (100 mg/kg or lower).

Table 8

Species	Route	LD_{50} (mg/kg)
Mouse	oral	403
	intraperitoneal	879
Rat	oral	1665
	intraperitoneal	763
	subcutaneous	≈ 20
Rabbit	dermal	> 5000
Monkey	oral	> 200
	intravenous infusion	≈ 8
	intravenous bolus	> 6

Irritation/Sensitization Studies

Skin irritation studies in rabbits showed that imiquimod was non-irritating when dosed unformulated at 500 mg or formulated up to 250 mg per site. Unformulated imiquimod produced mild or no eye irritation in rabbits when applied unformulated at 100 mg/eye or formulated up to 5 mg/eye. Formulated imiquimod was not irritating to rat or rabbit vaginal tract when applied every other day for 10 days at 10 and 50 mg/dose respectively. Dermal sensitization studies in guinea pigs showed that the imiquimod cream was not a dermal sensitizer. Comparison of the dermal reaction to imiquimod cream in animal species (rat, mouse, rabbit) with clinical study results, reveals that mouse and rabbit results are comparable to humans. The more severe dermal irritation seen in the rat is not predictive of human response.

Long-Term Toxicity
Two repeat dose dermal toxicity studies in rats showed a compound related but non-dose related dermal irritation. A dose-related decrease in body weight of male rats was also observed. No systemic toxicity was found at doses up to 5 mg/kg three days per week for 4 weeks or at doses up to 2.5 mg/kg three days per week for 16 weeks.

The adverse effects observed for the high doses (10-30 mg/kg) in repeat dose oral toxicity studies in rats and monkeys could be related to exaggerated pharmacological effects of excessive cytokines induction and lymphoid stimulation: reduced body weight gains, anaemia, serum protein changes and death. High repeat daily doses of imiquimod did not produce necrosis in any organ; the compound is not cytotoxic. Recovery animals demonstrated that the adverse effects were readily reversible. An oral no adverse effect level of 3 mg/kg/day was determined in both rats and monkeys dosed daily for 6 months.

Carcinogenicity
Two-year bioassays in Wistar rats (up to 3 mg/kg orally per day) and CD-1 mice (up to 4.5 mg/kg applied topically 3 times per week) showed no evidence of a carcinogenic effect in male and female rats and female mice. Liver tumours were increased in male mice exposed to the highest dose concentration, compared to the unexposed controls. However, the number of tumours was within the range seen historically for male CD-1 mice. It is generally accepted that an increase in liver tumours in male mice, in the absence of other neoplastic responses in mice or rats, is not indicative of a carcinogenic risk for humans.

In a photocarcinogenicity study in hairless mice, animals received imiquimod cream 3 times per week at concentrations of 0.03%, 0.1% and 0.3% and were irradiated with solar ultraviolet light for 5 days each week for 40 weeks and observed an additional 12 weeks. Vehicle cream enhanced UVR-induced skin tumour development. Imiquimod cream had no additional effect on tumour development beyond the vehicle effect (i.e., the addition of the active ingredient, imiquimod, to the vehicle cream did not result in an additional effect beyond the vehicle effect on tumour development).

Mutagenicity
Imiquimod was without effect in a series of eight mutagenicity assays including Ames, mouse lymphoma, CHO chromosome aberration, human lymphocyte chromosome aberration, SHE cell transformation, rat and hamster bone marrow cytogenetics, and mouse dominant lethal test.

Reproduction and Teratology
Teratology studies in rats and rabbits dosed at 1-20 mg/kg orally and at 0.5-2.0 mg/kg intravenously, did not reveal any teratogenic effects. The high doses in both studies produced some adverse effects in the dams related to maternal toxicity. The maternal toxicity was reflected in the high dose pups: reduced pup weights and delayed ossification in the rat. A radiolabel intravenous study in pregnant rabbits dosed at 1 mg/kg between day 6 to 18 of gestation for a total of 13 doses, showed radiolabel in the uteri, placenta, amniotic fluid and fetuses with no preferential concentration in the conceptus.

In a rat general reproduction study which utilized daily oral doses of 1.5-6.0 mg/kg, drug-related toxicity was observed at the high dose in the F_0 generation with no adverse reproductive effects.

Reversible ossification defects were observed in pups at the high dose. No effects were observed in growth, development, behaviour, learning/memory or reproduction of second generation. Daily oral administration of imiquimod to rats, at doses up to 8 times recommended human dose on a mg/m^2 basis throughout mating, gestation, parturition and lactation, demonstrated no impairment of reproduction.

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PART III: CONSUMER INFORMATION

PrZYCLARA®
Imiquimod Cream
2.5%, 3.75%

This leaflet is part III of a three-part "Product Monograph" published when ZYCLARA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZYCLARA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ZYCLARA is the brand name for imiquimod cream, 2.5% and 3.75%. It is used to treat actinic keratosis (AK) of the face or balding scalp in adults with normal immune systems.

What it does:
ZYCLARA is an immune response modifier. ZYCLARA is a medicine that works by stimulating your body's own immune response.

When it should not be used:
Do not use ZYCLARA if you are allergic to imiquimod, or other medications that contain imiquimod (e.g. ALDARA, VYLOMA), or any of the other ingredients in ZYCLARA.

What the medicinal ingredient is:
Imiquimod.

What the important nonmedicinal ingredients are:
Isostearic Acid, Cetyl Alcohol, Stearyl Alcohol, White Petrolatum, Polysorbate 60, Sorbitan Monostearate, Glycerin, Xanthan Gum, Purified Water, Benzyl Alcohol, Methylparaben, and Propylparaben.

What dosage forms it comes in:
ZYCLARA contains 25.0 mg imiquimod cream per gram (2.5%) or 37.5 mg imiquimod per gram (3.75%) and is supplied in pumps which contain 7.5 g of the cream and deliver 235 mg of the cream per actuation.

WARNINGS AND PRECAUTIONS

- ZYCLARA should not be used in patients under 18 years of age
- Avoid exposure to sunlight, sunlamp or tanning-bed during the treatment with ZYCLARA. Wear protective clothing and hat if you go outside during daylight
- ZYCLARA may cause severe skin reactions
- ZYCLARA may also cause flu-like symptoms before or during local skin reactions

BEFORE you use ZYCLARA talk to your doctor or pharmacist if:

- you have or had other skin cancers or other growths on your body
- you are immunocompromised (have weak immune system)
- you have or have had any other treatment for your actinic keratosis, such as freezing or surgery
- you are pregnant or planning to become pregnant
- you are breastfeeding or planning to breastfeed

ZYCLARA treatment is not recommended on areas larger than either the face or balding scalp.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about all the medicines you take or have taken, including prescription and non-prescription medicines, vitamins and herbal supplements. It is not known if ZYCLARA and other medicines can affect each other.

PROPER USE OF THIS MEDICATION

Use ZYCLARA exactly as prescribed by your doctor. Do not use ZYCLARA until your doctor has shown you the right way to use it.

Usual adult dose:
Apply ZYCLARA to the affected area(s) once a day just before bedtime.

Maximum daily dose is 500 mg (2 full actuations of the pump).

ZYCLARA should not be applied to areas larger than either the face or balding scalp.

The treatment consists of two 2-week treatment cycles, each cycle is separated by two weeks without treatment.

How to apply ZYCLARA pumps:

- Wash the area to be treated with mild soap and water. Allow the area to dry
- Wash your hands
- Before using the pump for the first time only, remove the cap and prime the pump by pressing the top of the pump all the way down (one or more times as needed) until the product appears. Discard this portion of the product
- Apply a thin layer of ZYCLARA ONLY to the affected area(s) to be treated. **Do not use more than two full pump actuations for each daily application**
- Rub the cream in all the way to the affected area(s). Avoid the cream in or around your eyes, lips and nostrils. If ZYCLARA accidentally gets in your mouth, your eyes, and nostrils rinse well with water right away
- Do not cover the treated area(s)

- After applying ZYCLARA, wash your hands well with soap and water
- Leave the cream on the affected area(s) for about 8 hours or as instructed by your doctor. Do not bathe or get the treated area(s) wet during the treatment period
- After the treatment period, wash the treated area(s) with mild soap and water
- When you have completed all of your doses as instructed, safely throw the pump away so that children and pets cannot get it.

Avoid exposure to sunlight, sunlamp or tanning-bed during the treatment with ZYCLARA.

Overdose:

In case of drug overdose, contact your doctor, or a poison control centre, or go to the emergency room of the hospital near you.

Missed Dose:
If you miss a dose of ZYCLARA, wait until the next night to apply it. Do not make up the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Possible side effects in the treatment area observed in studies of ZYCLARA include:

Actinic keratoses that were not seen before may appear during treatment.

Very common: redness, scabbing or crusting, flaking or dry skin, swelling, small open sores, drainage; itching, irritation, pain.

Uncommon: abnormal sensation, scarring.

Very rare: bleeding.

The side effects may go outside of the area where ZYCLARA was applied.

During treatment and until the skin has healed, your skin in the treatment area is likely to appear noticeably different from normal skin. If your skin breaks down, if sores develop during the first week of treatment, or if you get any skin reactions that affect your daily activities or do not go away, stop ZYCLARA right away and call your healthcare provider.

Sometimes, ZYCLARA must be stopped for a while to allow your skin to heal.

Other possible side effects observed in studies of ZYCLARA include:

Common: headache, tiredness, nausea, fever, loss of appetite, dizziness, herpes outbreak, pain, diarrhea, swollen lymph nodes, joint aches, skin irritation, difficulty sleeping.

Uncommon: chills, influenza-like symptoms, muscle aches, lack of energy, and itching.

Very rare: lip cracking, low blood counts.

If flu-like symptoms (fatigue, fever, muscle and joint pain, chills) develop after beginning treatment with ZYCLARA, contact your healthcare provider.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon			
Serious diarrhea		X	X
Very rare			
Serious low blood counts (pancytopenia)		X	X

These are not all the side effects of ZYCLARA. For more information, ask your healthcare provider or pharmacist.

HOW TO STORE IT

Store ZYCLARA between 15-25° C. Do not freeze.

Safely throw away ZYCLARA that is out of date or that you do not need.

Keep ZYCLARA and all medicines out of the reach of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be requested by contacting the sponsor, Bausch Health, Canada Inc., at: 1-800-361-4261.

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Last revised: October 29, 2020