PRODUCT MONOGRAPH

PrVYLOMA®

(imiquimod) Cream, 3.75% w/w

Immune response modifier

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(imiquimod) Cream, 3.75% w/w

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Cream / (3.75 % w/w), Available in a pump containing 7.5 g of cream	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

VYLOMA Cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata, whether present at the start of therapy or emerging during therapy, in immunocompetent adults.

Geriatrics (> 65 years of age)
Data from EGW clinical trials was too sparse to evaluate treatment effects in this population (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 VYLOMA Cream in immunosuppressed patients have not been established (See WARNINGS AND PRECAUTIONS, Immune). VYLOMA Cream should be used with caution in patients with pre-existing autoimmune conditions.

CONTRAINDICATIONS

VYLOMA 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 or to any components of the formulation (See WARNINGS AND PRECAUTIONS, Sensitivity). For a complete listing see the Dosage Forms, Composition and Packaging section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

Treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease is not recommended.

Local Inflammatory Reactions

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 VYLOMA Cream and may require an interruption of dosing (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

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

Severe local inflammatory reactions of the female external genitalia can lead to severe vulvar swelling. Severe vulvar swelling can lead to urinary retention. If severe vulvar swelling occurs, dosing should be interrupted or discontinued.

Administration of VYLOMA Cream is not recommended until the skin is healed from any previous drug or surgical treatment.

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 VYLOMA Cream may be temporarily interrupted and can be resumed after consultation with the treating physician, and once the skin reaction has subsided.

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).

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 to the treatment area(s) during treatment with VYLOMA.

Immune

The safety and efficacy of VYLOMA Cream in immunosuppressed patients have not been established. VYLOMA 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. VYLOMA Cream should be discontinued immediately if these events occur.

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 VYLOMA Cream is administered to nursing women.

Pediatrics (< 18 years of age)

Safety and efficacy in patients with external genital/perianal warts below the age of 18 years have not been established.

Geriatrics (> 65 years of age)

Of the 399 subjects treated with VYLOMA Cream in the EGW clinical studies, 5 subjects (1%) were 65 years or older. Data were too sparse to evaluate treatment effects in this population. 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

In controlled clinical trials the most frequently observed or reported adverse reactions were local skin and application site reactions, including erythema, edema, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, pain and irritation at the application site; some patients also reported systemic reactions. The incidence of adverse events, including treatment related and application site reactions, tended to be higher in women than in men. The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions. Both the incidence and severity of local skin reactions were significantly higher for the VYLOMA Cream in comparison to the placebo cream. Overall, 31.5% (126/400) patients treated with VYLOMA took rest periods, with more women taking a rest period than men. 1.5% (6/400) subjects discontinued the study due to safety reasons. Less than 2% (7/400) of patients reported serious adverse events, all of which were considered "not related" to the study drug by the investigator.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In two double-blind, placebo-controlled studies for genital warts, 602 subjects applied up to one packet of VYLOMA Cream or placebo daily for up to 8 weeks. The most frequently reported adverse reactions were local skin and application site reactions.

Overall, less than 1% (3/400) of the subjects treated with VYLOMA Cream discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical studies are shown in Table 1

Table 1: Local Skin Reactions in the Treatment Area Assessed by the Investigator

	VYLOMA Cream				**Placebo**			
	Females n=217		Males n=183		Females n=106		Males n=96	
	All Grades *	Severe	All Grades *	Severe	All Grades *	Severe	All Grades *	Severe
Any local skin reaction	77%	18%	82%	18%	33%	1%	41%	1%
Erythema	74%	10%	78%	10%	23%	0%	37%	1%
Edema (induration)	41%	2%	48%	2%	8%	0%	9%	0%
Weeping/ Exudate	35%	1%	39%	3%	5%	0%	0%	0%
Flaking/ Scaling/ Dryness	26%	0%	39%	0%	11%	0%	11%	0%
Scabbing/ Crusting	18%	<1%	34%	1%	6%	0%	2%	0%
Erosion/ Ulceration	36%	13%	42%	10%	7%	1%	2%	0%

*Mild, Moderate, or Severe

Local skin reactions were recorded as adverse events if they extended beyond the treatment area, if they required any medical intervention, or they resulted in patient discontinuation from the study.

Table 2: Females Only: Adverse Reactions Occurring in > 1% of VYLOMA-Treated Subjects and at a Greater Frequency than with Placebo in the Combined Studies

Preferred Term	VYLOMA Cream (N=217)	Placebo (N=106)
Female subjects with any adverse reaction	39.2%	36.8%
Application site pain	7.8%	0%
Application site irritation	5.5%	0.9%
Application site pruritus	3.2%	1.9%
Vaginitis bacterial	2.8%	1.9%
Headache	2.8%	0%
Back pain	1.8%	0.9%
Application site erythema	1.4%	0%
Application site bleeding	1.4%	0.9%
Application site discharge	1.4%	0%
Application site oedema	1.4%	0%

Table 3: Males Only: Adverse Reactions Occurring in >1% of VYLOMA-Treated Subjects and at a Greater Frequency than with Placebo in the Combined Studies

Preferred Term	VYLOMA Cream (N=183)	Placebo (N=96)
Male subjects with any adverse reaction	32.2%	17.7%
Application site irritation	6.6%	1.0%
Application site pain	6.0%	1.0%
Application site pruritus	2.2%	0%
Upper respiratory tract infection	2.2%	0%
Pruritus genital	1.6%	0%
Rash	1.6%	0%
Scrotal pain	1.6%	0%
Anxiety	1.1%	0%
Application site cellulitis	1.1%	0%
Application site excoriation	1.1%	0%
Application site rash	1.1%	0%
Application site reaction	1.1%	0%
Chest pain	1.1%	0%
Influenza	1.1%	1.0%
Pyrexia	1.1%	0%
Scrotal erythema	1.1%	0%
Scrotal oedema	1.1%	0%
Scrotal ulcer	1.1%	0%
Secretion discharge	1.1%	0%
Sinus congestion	1.1%	0%
Sinusitis	1.1%	0%
Skin exfoliation	1.1%	0%
Tinea cruris	1.1%	0%

Table 4: Application Site Reactions in Subjects by Gender*

	Females		Males	
Preferred Term	**VYLOMA Cream (n=217)**	**Placebo (n=106)**	**VYLOMA Cream (n=183)**	**Placebo (n=96)**
Subjects with any application site reaction	17.5%	3.8%	14.2%	1.0%
Application site pain	7.8%	0%	6.0%	1.0%
Application site irritation	5.5%	0.9%	6.6%	1.0%
Application site pruritus	3.2%	1.9%	2.2%	0%
Application site bleeding	1.4%	0.9%	0.5%	0%
Application site discharge	1.4%	0%	0.5%	0%
Application site erythema	1.4%	0%	0%	0%
Application site oedema	1.4%	0%	0%	0%
Application site cellulitis	0%	0%	1.1%	0%
Application site excoriation	0%	0%	1.1%	0%
Application site rash	0.9%	0%	1.1%	0%
Application site reaction	0.9%	0%	1.1%	0%
Application site vesicles	0.9%	0%	0.5%	0%
Application site dermatitis	0%	0%	0.5%	0%
Application site dryness	0%	0%	0.5%	0%
Application site erosion	0.5%	0%	0.5%	0%
Application site infection	0.5%	0%	0%	0%
Application site swelling	0.5%	0%	0%	0%
Application site ulcer	0.5%	0%	0.5%	0%

* Sorted by highest incidence rate in either gender

Adverse events considered potentially representative of the systemic effects of imiquimod or interferon-alpha induction (e.g., flu-like signs and symptoms, including malaise, fever, nausea, myalgia, and rigors) may accompany, or even precede, local inflammatory reactions with imiquimod treatment. A summary of these systemic symptoms from the combined studies is presented below in Table 5.

Table 5: Systemic Systems - Safety Populations

	VYLOMA Cream 3.75% (N=400)	Placebo (N=202)
Subjects with any systemic symptom	6.5%	4.0%
Headache	2.3%	0.5%
Nausea	1.8%	1.0%
Pyrexia	0.8%	0.5%
Influenza	0.8%	1.0%
Diarrhoea	0.5%	0.5%
Myalgia	0.5%	0%
Pain	0.5%	0.5%
Fatigue	0.5%	0%
Influenza like illness	0.3%	0%

Adverse events, additional to those reported with VYLOMA, are presented in Table 6 below, from clinical studies with ALDARA (5% imiquimod) cream for the treatment of EGW and from clinical studies with ZYCLARA (3.75% imiquimod) cream for the treatment of actinic keratoses (AK).

Table 6: Additional Adverse events reported in more than 1% of patients with 5% Imiquimod (for EGW)[a] and/or with 3.75% Imiquimod (for AK)[b] from Clinical Trials

SOC	Preferred Term
General disorders and administration site conditions	Application site discoloration
	Application site hypersensitivity
	Application site paraesthesia
	Application site scar
	Induration
	Soreness at wart site
	Tenderness
Blood and lymphatic system disorders	Lymphadenopathy
Cardiac disorders	Dizziness
Infections and infestations	Herpes simplex
Investigations	Blood glucose increased
Gastrointestinal disorders	Food poisoning
	Vomiting

Metabolism and nutrition disorders	Anorexia
Musculoskeletal and connective tissue disorders	Arthralgia
Neoplasms benign, malignant and unspecified	Seborrheic keratosis
	Squamous cell carcinoma
Psychiatric disorders	Insomnia
Skin and subcutaneous tissue disorders	Blister
	Dermatitis
	Papule
	Pruritus
	Skin burning sensation
	Skin haemorrhage

[a] adverse events judged to be possibly or probably related to ALDARA and reported in more than 1% of clinical trial patients in the treatment of EGW

[b] adverse events reported by more than 1% of ZYCLARA treated clinical trial patients and at a greater frequency than with Placebo in the treatment of actinic keratoses

Dermal Safety Trials Experience

Provocative repeat insult patch test studies involving induction and challenge phases produced no evidence that imiquimod cream causes photoallergenicity or contact sensitization in healthy skin; however, cumulative irritancy testing revealed the potential for imiquimod cream to cause irritation, and application site reactions were reported in the clinical studies.

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 ZYCLARA (imiquimod) Cream, 3.75% and 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, 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.

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

Respiratory: dyspnea.

Urinary System Disorders: proteinuria, urinary retention and dysuria.

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

Vascular: Henoch-Schoenlein purpura syndrome.

DRUG INTERACTIONS

Overview

Interactions between VYLOMA 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

VYLOMA Cream is not for oral, ophthalmic, intra-anal, or intravaginal use.

VYLOMA Cream should be applied once-a-day to the external genital/perianal warts. VYLOMA Cream should be used for up to 8 weeks.

Up to 1 full actuation of VYLOMA Cream should be applied to the treatment area at each application.

Missed Dose

If a dose is missed, the regular schedule should be continued. Do not make up the missed dose(s). Treatment should not be extended due to missed doses or rest periods.

Administration

Pump Administration

VYLOMA (imiquimod) Cream pumps should be primed before using for the first time by repeatedly depressing the actuator until cream is dispensed. It is not necessary to repeat this priming process during treatment.

VYLOMA Cream should be used as directed by a physician. VYLOMA Cream is for external use only. Contact with the eyes, lips and nostrils should be avoided.

It is recommended that patients wash their hands before and after applying VYLOMA Cream. VYLOMA Cream should be applied once-a-day to the external genital/perianal warts. VYLOMA Cream should be used for up to 8 weeks. **However, treatment should not be extended beyond 8 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 revaluated and management reconsidered. **VYLOMA Cream should be applied prior to normal sleeping hours and left on the skin for approximately 8 hours, after which time the cream should be removed by washing the area with mild soap and water**. The prescriber should demonstrate the proper application technique to maximize the benefit of VYLOMA Cream therapy.

A thin layer of VYLOMA Cream should be applied to the areas of existing and emerging warts and rubbed in until the cream is no longer visible. Up to 1 full actuation of the pump of VYLOMA Cream may be applied to the treatment area at each daily application. The application site should not be occluded. Following the treatment period, the cream should be removed by washing the treated area with mild soap and water. Partially-used pumps should be discarded and not reused.

Local skin reactions at the treatment site 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. Treatment may resume once the reaction subsides. Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions.
Sexual (genital, anal, oral) contact should be avoided while VYLOMA Cream is on the skin.
Application of VYLOMA 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.

Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

New warts may develop during therapy, as VYLOMA Cream is not a cure.

The effect of VYLOMA Cream on the transmission of genital/perianal warts is unknown.

VYLOMA Cream may weaken condoms and vaginal diaphragms, therefore concurrent use is not recommended.

Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water.

OVERDOSAGE

In case of drug overdose, including accidental ingestion, contact your doctor, local poison control centre or the nearest hospital emergency room, even if there are no symptoms.

Overdosage of VYLOMA 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 VYLOMA 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.

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

Imiquimod has no direct antiviral activity in cell culture. A study in 22 subjects with genital/perianal warts comparing imiquimod cream 5% and vehicle shows that imiquimod induces mRNA encoding cytokines including interferon-α at the treatment site. In addition, HPVL1 mRNA and HPV DNA are significantly decreased following treatment. However, the clinical relevance of these findings is

unknown.

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.

Systemic absorption of imiquimod (up to 9.4 mg) across the affected skin of 18 subjects with EGW was observed with once daily dosing for 3 weeks. The mean peak serum drug concentration at Day 21 was 0.488 ng/mL.

Special Populations and Conditions

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

Gender:
During 3 weeks of treatment, the AUC_{0-24} on Day 21 appeared to be similar in female and male subjects but C_{max} was higher and reached more quickly in female subjects who applied VYLOMA Cream to external genital warts.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

VYLOMA Cream is supplied as follows:

- Pump which contains 7.5 g of the cream.

Each actuation of the pump delivers 235 mg of cream.

Each gram of VYLOMA Cream contains 37.5 mg of imiquimod 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

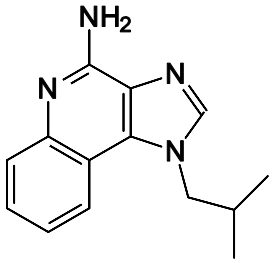
Common name: Imiquimod (USAN, INN)

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

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

Molecular mass: MW = 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

In two double-blind, randomized, placebo-controlled clinical studies, 601 subjects with EGW were treated with 3.75% imiquimod cream, or a matching placebo cream. Anatomic areas included: inguinal, perineal, and perianal areas (both genders); the glans penis, penis shaft/base, scrotum, and foreskin (in men); and the vulva/mons (in women). Up to one packet of study cream was applied once daily to each wart identified at Baseline and any new wart that appeared during the treatment period. The study cream was applied to all warts prior to normal sleeping hours and left on for approximately 8 hours. Subjects continued applying the study cream for up to 8 weeks or until they achieved complete clearance of all (baseline and new) warts in all anatomic areas. Subjects not achieving complete wart clearance by the Week 8 visit (end of treatment, EOT), were evaluated for up to 8 weeks or until they achieved complete clearance during an additional 8 week no-treatment period. Subjects who achieved complete clearance of all warts at any time until the Week 16 visit entered a 12-week follow-up for recurrence period.

Table 7: Patient Demographics in the Combined EGW Studies at Baseline

	VYLOMA Cream (N=399)	**Placebo (N=202)**
Age		
Mean (Minimum, Maximum)	32.7 (15.0, 81.0)	32.0 (18.0, 75.0)
Sex, n (%)		
Male	183 (45.9)	96 (47.5)
Female	216 (54.1)	106 (52.5)
Race, n (%)		
White	288 (72.2)	142 (70.3)
Black/African American	96 (24.1)	55 (27.2)
Other	15 (3.8)	5 (2.5)
Years Since EGW Diagnosis		
Mean (Minimum, Maximum)	4.6 (0.0, 39.4)	4.6 (0.0, 33.7)
Total wart area (mm^2)		
Median (Minimum, Maximum)	56 (9, 5579)	64 (6, 1969)
Mean (SD)	150.5 (394.2)	171.9 (321.2)
Total wart count		
Median (Minimum, Maximum)	6 (2, 48)	6 (2, 30)
Mean (SD)	8.6 (7.0)	9.6 (7.8)
Number of patients with anatomic areas affected with EGW, n (%)		
1 anatomic area	192 (48.1)	104 (51.5)
2 anatomic areas	146 (36.6)	68 (33.7)
3 anatomic areas	54 (13.5)	26 (12.9)
4 anatomic areas	7 (1.8)	4 (2.0)

Efficacy was assessed by wart counts (those present at Baseline and new warts appearing during the study) at EOS (i.e., up to 16 weeks from Baseline).

Complete clearance required clearance of all warts in all anatomic areas. Partial clearance rate was defined as the proportion of subjects with at least a 75% reduction in the number of baseline warts at EOS. Percent change in total number of warts as measured relative to the numbers of warts at EOS from Baseline. Complete and partial clearance rates, percent change in total number of warts from baseline to EOS and the numbers of subjects who remained clear of/recurred EGW at the end of the 12-week Follow-up for recurrence period are shown in the table below.

Table 8: Efficacy Endpoints

	VYLOMA Cream, 3.75%	**Placebo Cream**
Complete Clearance Rate*		
Overall	27.1%	8.7%
Females	35.5%	13.4%
Males	16.2%	3.1%
Partial Clearance Rate*		
Overall	38.1%	11.7%
Females	47.3%	16.7%
Males	26.9%	5.9%
Percent Change in Total Number of Warts from Baseline to End of Study (Mean, SD)		
Overall	-43.3% (52.41)	-8.6% (51.81)
Females	-54.4% (50.40)	-13.0% (59.84)
Males	-30.2% (51.83)	-3.7% (40.93)
Subjects who completely cleared and entered Follow-up, N	102	13
Subjects with sustained complete clearance	70% (71/102)	92% (12/13)
Subjects who recurred	16.7% (17/102)	0% (0/13)

*Adjusted for baseline wart count and wart area

DETAILED PHARMACOLOGY

Pharmacodynamics

Imiquimod is an immune response modifier that is not a nucleoside analogue. Imiquimod is a Toll-like receptor 7 agonist that activates immune cells. Topical application to skin is associated with increases in markers for cytokines and immune cells. 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.

Systemic absorption of imiquimod (up to 9.4 mg) across the affected skin of 18 subjects with EGW was observed with once daily dosing for 3 weeks. The mean peak serum drug concentration at Day 21 was 0.488 ng/mL.

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 9:

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 F0 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.

REFERENCES

1. ALDARA® (imiquimod) Cream, 5% Product Monograph, February 20, 2012, Medicis Pharmaceutical Corporation.

2. Arany I, Tyring S, Stanley MA, Tomai MA, Miller RL, Smith MH et al. Enhancement of the innate and cellular immune response in patients with genital warts treated with topical imiquimod cream 5%. Antiviral Res 1999;43:55-63.

3. Bernstein DI, Harrison CJ. Effects of the Immunomodulating Agent R-837 on Acute and Latent Herpes Simplex Virus Type 2 Infections. Antimicro Agents and Chemotherapy 1989; 33(9):1511-1515.

4. Bernstein DI, Miller RL, Harrison CJ. Effects of Therapy with an Immunomodulator (Imiquimod, R-837) Alone and with Acyclovir on Genital HSV-2 Infection in Guinea-Pigs When Begun After Lesion Development. Antiviral Res 1993; 20:45-55.

5. Dahl MV. Imiquimod: An immune response modifier. J Am Acad Dermatol 2000;43(1):S1-5.

6. Edwards L. Imiquimod in clinical practice. J Am Acad Dermatol 2000;43(1):S12-17.

7. Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL et al. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol 1998;134:25-30.

8. Gibson SJ, Lindh JM, Riter TR, et al. Plasmacytoid dendritic cells produce cytokines and mature in response to the TLR7 agonists, imiquimod and resiquimod. Cell Immunol. 2002;218(1-2):74-86.

9. Gollnick H, Barasso R, Jappe U, Ward K, Eul A, Carey-Yard M et al. Safety and efficacy of imiquimod 5% cream in the treatment of penile genital warts in uncircumcised men when applied three times weekly or once per day. Int J STD & AIDS 2001;12:22-28.

10. Harrison CJ, Miller RL, Bernstein DI. Posttherapy Suppression of Genital Herpes Simplex Virus (HSV) Recurrences and Enhancement of HSV-Specific T-Cell Memory by Imiquimod in Guinea Pigs. Antimicro Agents and Chemo 1994; 38(9):2059-2064.

11. Hemmi H, Kaisho T, Takeuchi O, Sato S, Sanjo H, Hoshino K, Horiuchi T, Tomizawa H, Takeda K, Akira S. Small anti-viral compounds activate immune cells *via* the TLR7 MyD88-dependent signaling pathway. Nat Immunol 2002; 3(2): 196-200.

12. Kende M, Lupton HW, Canonico PG. Treatment of Experimental Viral Infections with Immuno-modulators. Adv Biosci 1988; 68:51-63.

13. Miller RL, Birmachu W, Gerster JF et al. Imiquimod Cytokine Induction and Antiviral Activity. Intl Antiviral News 1995; 3(7):111-113.

14. Miller RL, Gerster JF, Owens ML, Slade HB, Tomai MA. Imiquimod applied topically: a novel immune response modifier and new class of drug. Int J Immunopharm 1999;21:1-14.

15. Sauder DN. Immunomodulatory and pharmacologic properties of imiquimods. J Am Acad Dermatol 2000;43(1):S6-11.

16. Testerman TL, Gerster JF, Imbertson LM et al. Cytokine Induction by the Immunomodulators Imiquimod and S-27609. J Leuk Biol 1995; 58:365-372.

17. Tyring SK. Immune-response modifiers: A new paradigm in the treatment of human papillomavirus. Curr Ther Res 2000;60(9):584-596.

18. Tyring SK, Arany I, Stanley MA, Tomai MA, Miller RL, Smith MH et al. A randomized, controlled, molecular study of condylomata acuminata clearance during treatment with imiquimod. J Infect Dis 1998;178(August):551-555.

19. Weeks CE, Gibson SJ. Induction of Interferon and Other Cytokines by Imiquimod and its Hydroxylated Metabolite R-842 in Human Blood Cells *In Vitro*. J Interferon Res 1994; 14:81-85.

20. ZYCLARA® (imiquimod) Cream, 3.75% Product Monograph, February 20, 2012, Medicis Pharmaceutical Corporation.

PART III: CONSUMER INFORMATION

PrVYLOMA®
(imiquimod) Cream, 3.75% w/w

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

ABOUT THIS MEDICATION

What the medication is used for:
VYLOMA is the brand name for imiquimod cream, 3.75%. It is used for the treatment of external genital and perianal warts/condyloma acuminata, whether present at the start of therapy or emerging during therapy, in immunocompetent adults.

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

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

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:
VYLOMA Cream contains 37.5 mg imiquimod per gram (3.75% w/w) and is supplied in a pump which contain 7.5 g of the cream and deliver 235 mg of the cream per actuation.

WARNINGS AND PRECAUTIONS

- VYLOMA should not be used in patients under 18 years of age
- Avoid exposure to of treated area(s) sunlight, sunlamp or tanning-bed during the treatment with VYLOMA.
- VYLOMA may cause severe skin reactions
- VYLOMA may also cause flu-like symptoms before or during local skin reactions
- VYLOMA may weaken condoms and vaginal diaphragms. An alternative form of contraception (birth control) should be used while using VYLOMA.
- It is not known whether VYLOMA has any effect on the transmission of warts. It is important to practice safe sex. Sexual contact (genital, oral, anal) should be avoided while the cream is on the skin. Talk to your doctor about safe sex practices.

BEFORE you use VYLOMA™ 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)
- if you are using other immunosuppressive drugs (See Interactions With This Medication)
- you have or have had any other treatment for your external genital/perianal warts, such as freezing or surgery
- you are pregnant or planning to become pregnant
- you are breastfeeding or planning to breastfeed

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, herbal supplements and immunosuppressants such as tacrolimus, pimecrolimus, cyclosporine, mycophenolate mofetil and methotrexate. Drug interaction studies have not been done with VYLOMA. It is not known if VYLOMA Cream and other medicines can affect each other.

PROPER USE OF THIS MEDICATION

Use VYLOMA Cream exactly as prescribed by your doctor. Do not use VYLOMA Cream until your doctor has shown you the right way to use it. VYLOMA Cream is not for oral, ophthalmic, intra-anal, or intravaginal use.

Usual adult dose:
Apply VYLOMA Cream to the external genital/perianal warts once a day just before bedtime.

VYLOMA Cream should be used for up to 8 weeks. **If there is no improvement, contact your doctor.**

How to apply VYLOMA Cream pump:
- Wash the area to be treated with mild soap and water. Allow the area to dry.
    - Uncircumcised males treating warts under their penis foreskin must pull their foreskin back and clean before treatment and clean daily during the weeks of treatment.
- 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 VYLOMA Cream **only** to affected area(s) to be treated. **Do not use more than one full pump actuation for each daily application**

- Rub the cream in all the way to the affected area or areas.
- Do not get VYLOMA Cream in or around your eyes or mouth. **If you get VYLOMA Cream in your mouth or in your eyes rinse well with water immediately.**
- Do not get VYLOMA in the anus when applying to perianal warts.
- Female patients treating genital warts must be careful when applying VYLOMA Cream around the vaginal opening. 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 cause pain or swelling and may cause problems passing urine. Do not put VYLOMA Cream in your vagina.
- Do not cover the treated area(s) with an airtight bandage. Cotton gauze dressings can be used. Cotton underwear can be worn after applying VYLOMA Cream to the genital or perianal area.
- After applying VYLOMA Cream, **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 before the right time has passed. Do not leave VYLOMA Cream on your skin longer than prescribed.
- After about 8 hours, 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.

Overdose:

In case of drug overdose, including accidental ingestion, contact your doctor, local poison control centre or the nearest hospital emergency room, even if there are no symptoms.

Missed Dose:
If you forget to apply VYLOMA Cream, continue on your regular schedule and do not make up the missed dose(s). Do not double dose(s). Treatment should not be extended beyond 8 weeks due to missed doses or rest periods.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects with VYLOMA Cream may include skin reactions at the treatment site such as:

- redness
- swelling
- a sore, blister, or ulcer
- pain
- irritation
- bleeding
- discharge
- skin that becomes hard or thickened
- skin peeling
- scabbing and crusting
- itching
- burning
- changes in skin color that do not always go away

Other side effects of VYLOMA Cream include pain, fever, muscle aches, and may also include headache, back pain, joint aches, tiredness, flu-like symptoms, nausea, and diarrhea.

During treatment and until the skin has healed, your skin in the treatment area is likely to appear noticeably different from normal skin. Side effects at the site where VYLOMA Cream is applied are common. Sometimes the side effects go outside of the area where VYLOMA Cream was applied. Patients should be aware that new warts may develop during treatment, as VYLOMA Cream may not be a cure. You have a higher chance for severe skin reactions if you use too much VYLOMA Cream or use it the wrong way. **Stop VYLOMA Cream right away and call your healthcare provider if you get any skin reactions that affect your daily activities, or that do not go away.** Sometimes, VYLOMA Cream must be stopped for a while to allow your skin to heal. Talk to your healthcare provider if you have questions about your treatment or skin reactions.

If the reactions seem excessive, if either skin breaks down or sores develop during the first week of treatment, if flu-like symptoms develop or if you begin to not feel well at any time, stop applying VYLOMA Cream and contact your healthcare provider.

Hypersensitivity (allergic) reactions have been reported for patients using imiquimod cream. If you develop allergic symptoms such as difficulty breathing, edema (swelling of mouth, throat, extremities), skin rash or skin reaction, discontinue the product, rinse off the cream, and contact your doctor immediately. These are not all the side effects of VYLOMA Cream. For more information, ask your healthcare provider or pharmacist.

HOW TO STORE IT

Store VYLOMA Cream between 15-25° C. Do not freeze. Safely throw away VYLOMA Cream that is out of date or that you do not need.

Keep VYLOMA Cream 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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