PRODUCT MONOGRAPH

PrAPO-IMIQUIMOD

Imiquimod Cream, 5% w/w

250 mg single-dose packet

Immune Response Modifier

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ACTION AND CLINICAL PHARMACOLOGY

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. The cytokine inducing properties of imiquimod may be responsible for its activity against genital/perianal warts, as imiquimod does not have a direct antiviral activity in cell cultures. The clinical relevance of these findings is, however, unknown.

Pharmacodynamics

Superficial Basal Cell Carcinoma (sBCC)
The mechanism of action of imiquimod in treating superficial basal cell carcinoma (sBCC) lesions is unknown. One clinical study in 6 subjects has suggested that imiquimod stimulates the infiltration of T-cell lymphocytes, dendritic cells, and macrophages into the basal cell carcinoma lesion.

Actinic Keratosis
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.

External Genital Warts
Imiquimod has no direct antiviral activity in cell culture. A study in 22 patients with genital/perianal warts comparing imiquimod 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 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 was observed across the affected skin of 12 patients with genital/perianal warts who were treated 3 times per week with sufficient 5% imiquimod cream to cover the affected wart area (average dose 4.6 mg imiquimod) for 16 weeks. Mean (median) peak drug concentrations of 0.3 (0.1) ng/mL were seen following week 16 dosing. Mean (median) urinary recoveries following the last dose of week 16, expressed as percent of the estimated applied dose, were 0.24 (0.09) and 2.52 (1.2) % of the dose for males and females, respectively, which may suggest a possible sex difference in absorption and/or excretion.

Similarly, systemic absorption of imiquimod across the affected skin of 58 patients with AK was observed with a dosing frequency of 3 applications per week for 16 weeks. Mean (median) peak serum drug concentrations at the end of week 16 were observed between 9 and 12 hours and were approximately 0.1 (0.1), 0.2 (0.2), and 3.5 (1.6) ng/mL for the applications to face (12.5 mg imiquimod, 1 single-use packet), scalp (25 mg, 2 packets) and hands/arms (75 mg, 6 packets), respectively. The application surface area was not controlled in the scalp and hands/arms groups. Dose proportionality was not observed, although the pharmacokinetic parameters (C_{max} and AUC) tended to increase with dose. It appears that systemic exposure may be more dependent on surface area of application than amount of applied dose. The apparent half-life following topical dosing was calculated as 26 hours, which is approximately 10 times greater than the 2 hour apparent half-life seen following subcutaneous dosing and suggests prolonged retention of drug in the skin. Mean (median) urinary recoveries at week 16 were 0.18 (0.14), 0.24 (0.24) and 0.12 (0.09) % of the applied dose following application to the face, scalp and hands/arms, respectively. The highest urinary recovery measured in any patient was less than 0.6% of the applied dose at week 16.

Comparative Clinical Bioequivalence Study

The purpose of this study was to determine the therapeutic equivalence of APO-IMIQUIMOD Cream, 5% (Apotex Inc.) with Aldara™ (Imiquimod) Cream, 5% (3M Pharmaceuticals Canada), in the treatment of subjects with Actinic Keratosis (AK), using 90% confidence interval of the difference and a 20% equivalence margin.

A double-blind, randomized, vehicle-controlled, multi-centre, parallel-group study was conducted in adult male and female subjects, at least 18 years of age, with 4 to 8 nonhyperkeratotic, nonhypertrophic AK lesions located within a contiguous 25 cm^2 area on the face or balding scalp. Patients applied study medication to the target treatment area twice weekly for 16 weeks and the primary efficacy endpoint was the complete clearance rate of AK lesions at Week 24 (8 weeks post-treatment). The efficacy results are summarized in the following table:

Complete Clearance Rate at Week 24 in Patients with Actinic Keratosis

Study Population Characteristic	Imiquimod 5%	Aldara™ 5%	Vehicle
Per Protocol Population			
N	106	100	63
Number and percent of patients with complete clearance at Week 24	49 (46.2%)	48 (48.0%)	9 (14.3%)
Difference (vs Aldara™) [a]	-1.8%		
90% CI [b]	(-14.2%, 10.6%)		
Modified Intent to Treat Population			
N	141	139	72
Number and percent of patients with complete clearance at Week 24, using LOCF [c]	62 (44.0%)	55 (39.6%)	9 (12.5%)
Difference (vs Aldara™) [a]	4.4%		
90% CI [b]	(-6.0%, 14.8%)		
Difference (vs vehicle) [d]	31.5%	27.1%	
p-value (vs vehicle) [e]	<0.0001	<0.0001	

NOTE: Complete clearance rate is the proportion of subjects with no clinically visible AK lesions within treatment target area at Week 24.
NOTE: Demonstrating therapeutic equivalence of the test formulation vs. reference treatment is based on the complete clearance rate at Week 24.
NOTE: The test for superiority of active treatment over the vehicle treatment is based on the complete clearance rate at Week 24.
a. Difference is the subtraction of the complete clearance rate at Week 24 of reference treatment from the test treatment.
b. 90% confidence interval of the difference calculated by Wald's Method with Yate's Continuity Correction.
c. LOCF: last-observation-carried-forward
d. Difference is the subtraction of the complete clearance rate at Week 24 of vehicle from each active treatment.
e. P-value comes from a Continuity-Corrected Z-Test.

APO-IMIQUIMOD cream 5% demonstrated therapeutic equivalence to Aldara™ 5% in complete clearance rate of lesions in subjects with Actinic Keratosis.

INDICATIONS AND CLINICAL USE

APO-IMIQUIMOD (imiquimod) cream is indicated in immunocompetent adults for the following conditions.

- Treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) with a maximum tumour diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), otherwise amenable to simple surgical excision, in patients who, in consultation with their physician, choose not to have surgery and are willing to undergo regular follow-up. Note: Surgical excision is the usual treatment of choice for these sBCC tumours. While imiquimod cream has been shown to be effective in the short-term clearance of sBCC in ~75% of cases, there are no data directly comparing imiquimod cream to surgical excision.

- Treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratosis on the face or balding scalp.

- Treatment of external genital and perianal warts/condyloma acuminata.

CONTRAINDICATIONS

APO-IMIQUIMOD (imiquimod) cream is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS

Patients with sBCC treated with imiquimod cream are required to have regular follow-up of the treatment site because the efficacy of imiquimod in the treatment of sBCC is generally less than that with surgery and, as well, because the long term efficacy and safety of imiquimod in the treatment of sBCC have not yet been established.

The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment since imiquimod cream has not been evaluated for the treatment of other types of basal cell carcinomas, including nodular, morpheaform (fibrosing or sclerosing) types and is not recommended for treatment of BCC subtypes other than the superficial variant.

Imiquimod cream has not been evaluated for the treatment of sBCC on the face, head, hands or feet, and anogenital area.

The efficacy of imiquimod cream in the prevention of squamous cell carcinoma (SCC) associated with AK has not been established. One subject who participated in a clinical trial of imiquimod and had complete clearance of AK lesions with imiquimod treatment developed a SCC *in situ* in the treatment area within 12 to 18 months of treatment (see PHARMACOLOGY, Clinical Studies).

Imiquimod cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and is not recommended for these conditions.

Hypersensitivity reactions (urticaria) and erythema multiforme have been reported in patients receiving imiquimod cream. Causality has not been established and no other reports of similar cases have been reported in post-marketing surveillance. Imiquimod cream should be discontinued immediately if these events occur.

Some reports of localised hypopigmentation and hyperpigmentation following use of imiquimod cream have been received. Post-marketing reporting suggests that these skin colour changes may be permanent in some patients.

PRECAUTIONS

General

Imiquimod cream administration is not recommended until skin or genital/perianal tissue is healed from any previous drug or surgical treatment. Imiquimod cream has the potential to exacerbate inflammatory conditions of the skin.

Local skin reactions such as erythema, erosion, excoriation/flaking, and edema are common.

Should a severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with imiquimod cream can be resumed after the skin reaction has subsided.

The efficacy and safety of imiquimod cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum.

The safety of imiquimod cream applied to areas of skin greater than 25 cm^2 for the treatment of actinic keratosis has not been established.

The safety and efficacy of imiquimod cream in immunosuppressed patients have not been established.

Flu-like systemic signs and symptoms including malaise, fever, nausea, myalgias and rigors may occur. Dosing interruption may be required.

Imiquimod cream should be used with caution in patients with pre-existing autoimmune conditions. Rare reports have been received of exacerbation of autoimmune conditions in patients treated with imiquimod cream.

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

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of imiquimod cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (hat) when using imiquimod cream. Patients with sunburn should be advised not to use imiquimod 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 imiquimod cream. Phototoxicity has not been adequately assessed for imiquimod cream. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (*see PHARMACOLOGY, Clinical Studies*), imiquimod cream shortened the time to skin tumour formation in an animal photoco-carcinogenicity study (*see Carcinogenesis, Mutagenesis, Impairment of Fertility*). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

Carcinogenicity, Mutagenesis, and Impairment of Fertility: 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 imiquimod 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).

Pregnancy: 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 clearly needed.

Nursing Mothers: It is not known whether topically applied imiquimod is excreted in breast milk.

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

Geriatric Use: Although no overall differences in safety or effectiveness have been observed between elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. Of the 185 patients in the 5 times per week treatment groups of clinical studies evaluating the treatment of sBCC with imiquimod cream, 65 patients (35%) were 65 years and older, while 25 patients (14%) were 75 years and older. Of the 215 patients in the 2 times per week clinical studies evaluating the treatment of AK lesions with imiquimod cream, 127 patients (59%) were 65 years and older, while 60 patients (28%) were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients. No other clinical experience has identified differences in responses between the elderly and younger patients.

DRUG INTERACTIONS

Interactions between imiquimod 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, pimicrolimus, mycophenolate mofetil, cyclosporine or methotrexate.

Concomitant use of corticosteroids with imiquimod may potentially limit efficacy.

ADVERSE REACTIONS

Superficial Basal Cell Carcinoma

The data described below reflect exposure to imiquimod cream or vehicle in 364 patients enrolled in two double-blind, vehicle-controlled studies in which subjects with sBCC applied imiquimod cream or vehicle to the target lesions 5X/week for 6 weeks.

Summary of All Adverse Events Reported by >1% of Patients in the Combined 5X/Week Studies				
BODY SYSTEM PREFERRED TERM	**Imiquimod 5X/Week (n = 185)**		**Vehicle 5X/Week (n = 179)**	
APPLICATION SITE DISORDERS				
APPLICATION SITE REACTION	52	(28.1%)	5	(2.8%)
BODY AS A WHOLE - GENERAL DISORDERS				
ALLERGY AGGRAVATED	2	(1.1%)	1	(0.6%)
BACK PAIN	7	(3.8%)	1	(0.6%)
CHEST PAIN	2	(1.1%)	0	(0.0%)
FATIGUE	4	(2.2%)	2	(1.1%)
FEVER	3	(1.6%)	0	(0.0%)
PAIN	3	(1.6%)	2	(1.1%)
CARDIOVASCULAR DISORDERS, GENERAL				
HYPERTENSION	5	(2.7%)	1	(0.6%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	2	(1.1%)	1	(0.6%)
DIZZINESS	14	(7.6%)	4	(2.2%)
HEADACHE				
GASTRO-INTESTINAL SYSTEM DISORDERS				
ABDOMINAL PAIN	1	(0.5%)	2	(1.1%)
DIARRHEA	1	(0.5%)	2	(1.1%)
DYSPEPSIA	3	(1.6%)	2	(1.1%)
GASTRO-INTESTINAL DISORDER NOS	1	(0.5%)	2	(1.1%)
NAUSEA	2	(1.1%)	0	(0.0%)
TOOTH DISORDER	0	(0.0%)	2	(1.1%)
METABOLIC AND NUTRITIONAL DISORDERS				
GOUT	2	(1.1%)	0	(0.0%)
MUSCULO-SKELETAL SYSTEM DISORDERS				
SKELETAL PAIN	3	(1.6%)	2	(1.1%)
PSYCHIATRIC DISORDERS				
ANXIETY	2	(1.1%)	1	(0.6%)
RESISTANCE MECHANISM DISORDERS				
INFECTION	1	(0.5%)	3	(1.7%)
INFECTION FUNGAL	2	(1.1%)	2	(1.1%)
RESPIRATORY SYSTEM DISORDERS				
COUGHING	3	(1.6%)	1	(0.6%)
PHARYNGITIS	2	(1.1%)	1	(0.6%)
RHINITIS	5	(2.7%)	1	(0.6%)
SINUSITIS	4	(2.2%)	1	(0.6%)
UPPER RESPIRATORY TRACT INFECTION	6	(3.2%)	2	(1.1%)
SECONDARY TERMS				
INFLICTED INJURY	3	(1.6%)	3	(1.7%)
PROCEDURAL SITE REACTION	2	(1.1%)	3	(1.7%)
SKIN AND APPENDAGE DISORDERS				
HYPERKERATOSIS	3	(1.6%)	2	(1.1%)
RASH	3	(1.6%)	1	(0.6%)
SKIN DISORDER	1	(0.5%)	3	(1.7%)
WHITE CELL AND RESISTANCE DISORDER				
LYMPHADENOPATHY	5	(2.7%)	1	(0.6%)

The most frequently reported adverse reactions were those of local skin and application site reactions including erythema, edema, induration, erosion, flaking/scaling, scabbing/crusting, itching and burning at the application site. The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions; 10% (19/185) of patients received rest periods. The average number of doses not received per patient due to rest periods was 7 doses with a range of 2 to 22 doses; 79% of patients (15/19) resumed therapy after a rest period. Overall, in the clinical studies, 2% (4/185) of patients discontinued for local skin/application site reactions. The incidence of application site reactions reported by >1% of the subjects during the 6-week treatment period is summarized in the table below.

Summary of All Application Site Reactions Reported by >1% of Patients in the Combined 5X/Week Studies

Included Term	Imiquimod 5X/Week (n = 185)		Vehicle 5X/Week (n = 179)	
ITCHING AT TARGET SITE	30	(16.2%)	1	(0.6%)
BURNING AT TARGET SITE	11	(5.9%)	2	(1.1%)
PAIN AT TARGET SITE	6	(3.2%)	0	(0.0%)
TENDERNESS AT TARGET SITE	2	(1.1%)	0	(0.0%)
ERYTHEMA AT REMOTE SITE	3	(1.6%)	0	(0.0%)
PAPULE(S) AT TARGET SITE	3	(1.6%)	0	(0.0%)
BLEEDING AT TARGET SITE	4	(2.2%)	0	(0.0%)
TINGLING AT TARGET SITE	1	(0.5%)	2	(1.1%)
INFECTION AT TARGET SITE	2	(1.1%)	0	(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 incidence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Most Intense Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Percentage of Patients) 5X/Week Application

Local Skin Reaction	Mild/Moderate		Severe	
	Imiquimod Cream (n = 184)	Vehicle (n = 178)	Imiquimod Cream (n = 184)	Vehicle (n = 178)
EDEMA	71%	36%	7%	0%
EROSION	54%	14%	13%	0%
ERYTHEMA	69%	95%	31%	2%
FLAKING/SCALING	87%	76%	4%	0%
INDURATION	78%	53%	6%	0%
SCABBING/CRUSTING	64%	34%	19%	0%
ULCERATION	34%	3%	6%	0%
VESICLES	29%	2%	2%	0%

Adverse events judged to be probably or possibly related to imiquimod cream and reported by at least 1% of the patients included:

Application Site Reactions

Target Site Reactions: Itching, burning, pain, tenderness, bleeding, papules, infection, pimples;

Remote Site Reactions: Erythema

Body as a Whole
Back pain

White Cell and Resistance Disorders
Lymphadenopathy

In the sBCC studies, 23 of 1266 (1.8%) imiquimod-treated patients developed treatment site infections that were treated with antibiotics; the majority of these patients required a rest period off imiquimod cream. In all vehicle controlled BCC studies, the adverse event lymphadenopathy was reported in 12 (1.8%) of the 672 imiquimod-treated patients. In all phase II/III BCC trials with 5X/week imiquimod dose groups, 9 (1.7%) of 518 patients with pre- and post-treatment laboratory tests developed a ≥2 toxicity grade level shift from baseline to end-of-treatment in absolute lymphocyte counts.

Actinic Keratosis

The data described below reflect exposure to imiquimod cream or vehicle in 436 patients enrolled in two double-blind, vehicle-controlled studies in which patients applied imiquimod cream or vehicle to a 25 cm^2 contiguous treatment area on the face or balding scalp 2 times per week for 16 weeks.

In controlled clinical studies, the most frequently reported adverse reactions were those of local skin and application site reactions including erythema, flaking/scaling/dryness, scabbing/crusting, itching and burning at the application site. The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions: 16% (35/215) of patients received rest periods. The average number of doses not received per patient due to rest periods was 4 doses with a range of 1 to 11 doses: 91% of patients (32/35) resumed therapy after a rest period. Overall, in the clinical studies, 2% (5/215) of patients discontinued for local skin/application site reactions and one patient discontinued due to the development of urticaria. One patient developed a bacterial infection at the treatment site.

Summary of All Adverse Events Reported by >1% of Patients in the Combined 2X/Week Studies

BODY SYSTEM PREFERRED TERM	Imiquimod 2X/Week (n = 215)		Vehicle 2X/Week (n = 221)	
APPLICATION SITE DISORDERS				
APPLICATION SITE REACTION	71	(33.0%)	32	(14.5%)
BODY AS A WHOLE - GENERAL DISORDERS				
BACK PAIN	3	(1.4%)	2	(0.9%)
FATIGUE	3	(1.4%)	2	(0.9%)
FEVER	3	(1.4%)	0	(0.0%)
HEADACHE	11	(5.1%)	7	(3.2%)
HERNIA NOS	4	(1.9%)	1	(0.5%)
INFLUENZA-LIKE SYMPTOMS	4	(1.9%)	4	(1.8%)
PAIN	3	(1.4%)	3	(1.4%)
RIGORS	3	(1.4%)	0	(0.0%)
CARDIOVASCULAR DISORDERS, GENERAL				

Summary of All Adverse Events Reported by >1% of Patients in the Combined 2X/Week Studies				
BODY SYSTEM PREFERRED TERM	**Imiquimod 2X/Week (n = 215)**		**Vehicle 2X/Week (n = 221)**	
CHEST PAIN	1	(0.5%)	4	(1.8%)
HYPERTENSION	3	(1.4%)	5	(2.3%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS DIZZINESS	3	(1.4%)	1	(0.5%)
GASTRO-INTESTINAL SYSTEM DISORDERS				
DIARRHEA	6	(2.8%)	2	(0.9%)
DYSPEPSIA	6	(2.8%)	4	(1.8%)
GASTROESOPHAGEAL REFLUX	3	(1.4%)	3	(1.4%)
NAUSEA	3	(1.4%)	3	(1.4%)
VOMITING	3	(1.4%)	1	(0.5%)
HEART RATE AND RHYTHM DISORDERS				
FIBRILLATION ATRIAL	3	(1.4%)	2	(0.9%)
METABOLIC AND NUTRITIONAL DISORDERS				
HYPERCHOLESTEROLEMIA	4	(1.9%)	0	(0.0%)
MUSCULO-SKELETAL SYSTEM DISORDERS				
ARTHRALGIA	2	(0.0%)	4	(1.8%)
ARTHRITIS	2	(0.9%)	3	(1.4%)
MYALGIA	3	(1.4%)	3	(1.4%)
SKELETAL PAIN	1	(0.5%)	3	(1.4%)
NEOPLASM				
BASAL CELL CARCINOMA	5	(2.3%)	5	(2.3%)
CARINOMA SQUAMOUS	8	(3.7%)	5	(2.3%)
RESISTANCE MECHANISM DISORDERS	9	(4.2%)	11	(5.0%)
HERPEX SIMPLEX	4	(1.9%)	4	(1.8%)
INFECTION VIRAL	3	(1.4%)	2	(0.9%)
RESPIRATORY SYSTEM DISORDERS				
BRONCHITIS	2	(0.9%)	3	(1.4%)
COUGHING	6	(2.8%)	10	(4.5%)
PHARYNGITIS	4	(1.9%)	4	(1.8%)
PULMONARY CONGESTION	1	(0.5%)	3	(1.4%)
RHINITIS	7	(3.3%)	8	(3.6%)
SINUSITIS	16	(7.4%)	14	(6.3%)
UPPER RESPIRATORY TRACT INFECTION	33	(15.3%)	27	(2.2%)
SECONDARY TERMS				
ABRASION NOS	7	(3.3%)	5	(2.3%)
CYST NOS	0	(0.0%)	4	(1.8%)
INFLICTED INJURY	19	(8.8%)	21	(9.5%)
POST-OPERATIVE PAIN	3	(1.4%)	4	(1.8%)
SKIN AND APPENDAGES DISORDERS	47	(21.9%)	42	(19.0%)
ALOPECIA	3	(1.4%)	0	(0.0%)
DERMATITIS	3	(1.4%)	7	(3.2%)
ECZEMA	4	(1.9%)	3	(1.4%)
HYPERKERATOSIS	19	(8.8%)	12	(5.4%)
PHOTOSENSITIVITY REACTION	2	(0.9%)	4	(1.8%)
PRURITUS	2	(0.9%)	3	(1.4%)
RASH	5	(2.3%)	5	(2.3%)
SKIN DISORDER	6	(2.8%)	7	(3.2%)
VERRUCA	1	(0.5%)	3	(1.4%)
URINARY SYSTEM DISORDERS	8	(3.7%)	10	(4.5%)

Summary of All Adverse Events Reported by >1% of Patients in the Combined 2X/Week Studies				
BODY SYSTEM PREFERRED TERM	**Imiquimod 2X/Week (n = 215)**		**Vehicle 2X/Week (n = 221)**	
URINARY TRACT INFECTION	3	(1.4%)	1	(0.5%)
VISION DISORDERS				
CONJUNCTIVITIS	1	(0.5%)	3	(1.4%)
EYE ABNORMALITY	4	(1.9%)	1	(0.5%)
EYE INFECTION	0	(0.0%)	3	(1.4%)

Summary of All Application Site Reactions Reported by >1% of Patients in the Combined 2X/Week Studies				
Included Term	**Imiquimod 2X/Week (n = 215)**		**Vehicle 2X/Week (n = 221)**	
BLEEDING AT TARGET SITE	7	(3.3%)	1	(0.5%)
BURNING AT REMOTE SITE	4	(1.9%)	0	(0.0%)
BURNING AT TARGET SITE	12	(5.6%)	4	(1.8%)
INDURATION AT REMOTE SITE	3	(1.4%)	0	(0.0%)
INDURATION AT TARGET SITE	5	(2.3%)	3	(1.4%)
IRRITATION AT REMOTE SITE	3	(1.4%)	0	(0.0%)
ITCHING AT REMOTE SITE	7	(3.3%)	3	(1.4%)
ITCHING AT TARGET SITE	44	(20.5%)	15	(6.8%)
PAIN AT TARGET SITE	5	(2.3%)	2	(0.9%)
STINGING AT TARGET SITE	6	(2.8%)	2	(0.9%)
TENDERNESS AT TARGET SITE	4	(1.9%)	3	(1.4%)

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.

Most Intense Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Percentage of Patients) 2X/Week Application				
	Mild/Moderate		**Severe**	
Event	**Imiquimod Cream (n = 215)**	**Vehicle (n = 220)**	**Imiquimod Cream (n = 215)**	**Vehicle (n = 220)**
Erythema	80%	91%	18%	2%
Edema	49%	10%	0%	0%
Weeping/Exudate	21%	1%	0%	0%
Vesicles	9%	1%	0%	0%
Erosion/Ulceration	46%	9%	2%	0%
Flaking/Scaling/Dryness	85%	87%	7%	3%
Scabbing/Crusting	70%	40%	8%	2%

External Genital Warts

In controlled clinical trials, the most frequently reported adverse reactions were those of local skin and application site reactions; some patients also reported systemic reactions. These reactions were usually mild to moderate in intensity; however, severe reactions were reported with 3 times per week application. **These reactions were more frequent and more intense**

with daily application than with 3 times per week application. Overall, in the 3 times per week application clinical studies, 1.2% (4/327) of the patients discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.

Wart Site Reaction as Assessed by Investigator (3X/Week Application)								
	Mild/Moderate				**Severe**			
	Females		**Males**		**Females**		**Males**	
	Imiquimod Cream (n = 114)	**Vehicle (n = 99)**	**Imiquimod Cream (n = 156)**	**Vehicle (n = 157)**	**Imiquimod Cream (n = 114)**	**Vehicle (n = 99)**	**Imiquimod Cream (n = 156)**	**Vehicle (n = 157)**
Erythema	61%	21%	54%	22%	4%	0%	4%	0%
Erosion	30%	8%	29%	6%	1%	0%	1%	0%
Excoriation/ Flaking	18%	8%	25%	8%	0%	0%	1%	0%
Edema	17%	5%	12%	1%	1%	0%	0%	0%
Induration	5%	2%	7%	2%	0%	0%	0%	0%
Ulceration	5%	1%	4%	1%	3%	0%	0%	0%
Scabbing	4%	0%	13%	3%	0%	0%	0%	0%
Vesicles	3%	0%	2%	0%	0%	0%	0%	0%

Remote site skin reactions were also reported in female and male patients treated 3 times a week with imiquimod cream. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%).

Adverse events judged to be probably or possibly related to imiquimod cream reported by more than 5% of patients are listed below; also included are soreness, influenza-like symptoms and myalgia.

Adverse Events Probably or Possibly Related to Imiquimod Cream (3X/Week Application)				
	Females		**Males**	
	Imiquimod Cream (n = 117)	**Vehicle (n = 103)**	**Imiquimod Cream (n = 156)**	**Vehicle (n = 158)**
APPLICATION SITE DISORDERS:				
APPLICATION SITE REACTIONS **Wart Site:**				
Itching	32%	20%	22%	10%
Burning	26%	12%	9%	5%
Pain	8%	2%	2%	1%
Soreness	3%	0%	0%	1%
FUNGAL INFECTION*	11%	3%	2%	1%
SYSTEMIC REACTIONS:				
Headache	4%	3%	5%	2%
Influenza-like symptoms	3%	2%	1%	0%
Myalgia	1%	0%	1%	1%

* Incidences reported without regard to causality with imiquimod cream.

Adverse events judged to be possibly or probably related to imiquimod cream and reported by more than 1% of patients include:

Application Site Disorders

Wart Site Reactions: Burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness; ***Remote Site Reactions:*** Bleeding, burning, itching, pain, tenderness, tinea cruris

Body as a Whole
Fatigue, fever, influenza-like symptoms

Central and Peripheral Nervous System Disorders
Headache

Gastro-Intestinal System Disorders
Diarrhea

Musculo-Skeletal System Disorders
Myalgia

Post-Marketing Experience:

Application Site Disorders (resulting from internal application): Local skin reactions, pain and swelling, difficulty passing urine in female patients.

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

The following adverse reactions have been identified during post-approval use of 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

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

Skin and Appendages: Exfoliative dermatitis, erythema multiforme, hyperpigmentation, hypertrophic scar

Vascular: Henoch-Schonlein purpura syndrome

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage of imiquimod 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 imiquimod cream cream could result in severe local skin 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.

DOSAGE AND ADMINISTRATION

The application frequency for APO-IMIQUIMOD (imiquimod cream) is different for each indication.

Superficial Basal Cell Carcinoma

APO-IMIQUIMOD (imiquimod cream) is to be applied to a biopsy-confirmed sBCC 5 times per week, prior to normal sleeping hours, and left on the skin for approximately 8 hours. The

treatment area should include a 1 cm margin of skin around the tumour. The amount of cream to be applied depends upon the diameter of the target sBCC (see table below)

Patient Dosing Guide		
Target Tumour Diameter	**Size of Cream Droplet to be Used (diameter)**	**Approximate Amount of Cream to be Used**
0.5 to <1.0 cm	4 mm	10 mg
≥1.0 to <1.5 cm	5 mm	25 mg
≥1.5 to 2.0 cm	7 mm	40 mg

Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly. The cream should be applied to cover the treatment area, including one centimetre of skin surrounding the tumour, and should be rubbed into the treatment area until the cream is no longer visible. Caution subjects to avoid contacting the cream in or near the eyes. Approximately 8 hours after applying APO-IMIQUIMOD, cream should be removed by washing the area with mild soap and water. An example of a 5 times per week application schedule is to apply APO-IMIQUIMOD cream once per day, Monday through Friday, prior to sleeping hours.

APO-IMIQUIMOD cream treatment should continue for 6 weeks. Local skin reactions in the treatment area are common. Patients should contact their physician if they experience any sign or symptom in the treatment area that restricts or prohibits their daily activity or makes continued application of the cream difficult. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. However, the treatment period should not be extended beyond 6 weeks due to missed doses or rest periods.

The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of APO-IMIQUIMOD cream therapy. Hand washing before and after cream application is recommended. The application site is not to be occluded.

A follow-up visit at approximately 12 weeks post-treatment to assess the treatment site for clinical clearance is appropriate. Early clinical clearance cannot be adequately assessed until resolution of local skin reactions. If there is clinical evidence of persistent tumour at the 12-week post-treatment visit, a biopsy or other alternative intervention should be considered; the safety of and efficacy of a repeat course of imiquimod cream treatment have not been established. If any suspicious lesion arises in the treatment area at any time after 12 weeks, the patient should seek a medical evaluation.

APO-IMIQUIMOD cream is packaged in single-use packets which contain 250 mg of the cream. No more than one sixth of a packet of APO-IMIQUIMOD cream should be applied to the treatment area at each application. Partially-used packets should be discarded and not reused.

Actinic Keratosis

APO-IMIQUIMOD cream is to be applied 2 times per week to a defined treatment area on the face or scalp no larger than 25 cm^2, prior to normal sleeping hours, and left on the skin for

approximately 8 hours. Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly. The cream should be rubbed into the treatment area until the cream is no longer visible. Contact with the eyes, lips and nostrils should be avoided. Following the treatment period, cream should be removed by washing the area with mild soap and water. Examples of two times per week application schedules are Monday and Thursday, or Tuesday and Friday prior to sleeping hours.

APO-IMIQUIMOD cream treatment should continue for 16 weeks. Local skin reactions in the treatment area are common. Patients should contact their physician if they experience any sign or symptom in the treatment area that restricts or prohibits their daily activity or makes continued application of the cream difficult. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.

The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of APO-IMIQUIMOD cream therapy. Hand washing before and after cream application is recommended.

APO-IMIQUIMOD cream is packaged in single-use packets. No more than one packet of APO-IMIQUIMOD cream should be applied to the treatment area at each application. Partially-used packets should be discarded and not reused. The application site is not to be occluded.

External Genital Warts

APO-IMIQUIMOD (imiquimod) cream is to be applied 3 times per week, prior to normal sleeping hours, and left on the skin for 6-10 hours. Following the treatment period cream should be removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours.

APO-IMIQUIMOD cream treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks. Local skin reactions (erythema) at the treatment site are common. A rest period of several days may be taken if required by the patient due to 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.

The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of APO-IMIQUIMOD cream therapy. Hand washing before and after cream application is recommended.

APO-IMIQUIMOD cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm^2; use of excessive amounts of cream should be avoided. Patients self-administer APO-IMIQUIMOD cream by applying the cream to external genital and/or perianal warts. A thin layer is applied to the wart area and rubbed in until the cream is no longer visible. The application site is not to be occluded.

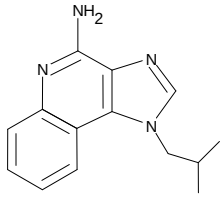
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Imiquimod (USAN, INN)

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

Structural Formula:



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

Molecular Weight: 240.3

Description: White to off-white crystalline powder.

Solubility: Insoluble in water, methanol and acetonitrile but soluble in dimethylsulfoxide (3 mg/mL) and dimethyl formamide.

pKa Value: 7.3

Polymorphism: No polymorphs are reported for imiquimod in literature to date.

Partition Coefficient: LogP = 3.01

Hygroscopicity: Not hygroscopic

Melting Point: 292-294°C

Composition:

Each gram of APO-IMIQUIMOD (imiquimod) cream contains 50 mg of imiquimod in a cream base consisting of benzyl alcohol, cetyl alcohol, glycerin, isostearic acid, methylparaben, polysorbate 60, propylparaben, purified water, sorbitan monostearate, stearyl alcohol, white petrolatum, and xanthan gum.

Stability and Storage Recommendations:

Store between 20-25°C (68°F to 77°F). Avoid freezing.

AVAILABILITY OF DOSAGE FORMS

APO-IMIQUIMOD (Imiquimod Cream) is available in single-use packets which contain 250 mg of the cream. It is available as a box of 12 or 24 packets.

INFORMATION FOR THE CONSUMER

Please read this before using APO-IMIQUIMOD (imiquimod) cream and talk to your doctor, the nurse or your pharmacist if you have any questions about how to use APO-IMIQUIMOD cream.

1. What is APO-IMIQUIMOD cream?

APO-IMIQUIMOD (imiquimod) cream is a brand name for imiquimod cream. APO-IMIQUIMOD cream is used in immunocompetent adults to treat the following conditions.

- Biopsy-confirmed, primary Superficial Basal Cell Carcinoma (sBCC) located on the trunk (excluding external genital and perianal skin), neck, or extremities (excluding hands and feet).
- Actinic Keratosis (AK)
- External Genital/Perianal Warts (EGW) caused by the human papillomavirus (HPV).

APO-IMIQUIMOD cream can only be used if a doctor prescribes it for you.

APO-IMIQUIMOD cream should only be used on the skin.

APO-IMIQUIMOD cream is manufactured by Apotex Inc. It is a white cream containing 50 mg of imiquimod per gram.

2. What other ingredients are in APO-IMIQUIMOD cream?

APO-IMIQUIMOD cream also contains: benzyl alcohol, cetyl alcohol, glycerin, isostearic acid, methylparaben, polysorbate 60, propylparaben, purified water, sorbitan monostearate, stearyl alcohol, white petrolatum and xanthan gum.

3. What packages is APO-IMIQUIMOD cream sold in?

APO-IMIQUIMOD cream is supplied in single-use packets which contain 250 mg of the cream. It is available as a box of 12 or 24 packets.

4. How does APO-IMIQUIMOD cream work?

APO-IMIQUIMOD cream is an immune response modifier. APO-IMIQUIMOD cream is a medicine that works by stimulating your body's own immune response.

5. What should I tell my doctor before using APO-IMIQUIMOD cream?

Allergies

- Tell your doctor if you have ever had any unusual or allergic reaction to imiquimod cream.
- Tell your doctor or the nurse or pharmacist if you have any allergies.

Pregnancy
- Tell your doctor if you are planning to become pregnant.
- Tell your doctor if you are pregnant (about to have a baby).
- Tell your doctor if you are breast-feeding your baby.

APO-IMIQUIMOD cream should not be used while pregnant or breast-feeding unless your doctor tells you to.

Previous treatment
Tell your doctor and pharmacist of any other treatment you have had for your Superficial Basal Cell Carcinoma, Actinic Keratosis or External Genital/Perianal Warts including:
- any prescription and over-the-counter drugs you have used.
- any other non-drug treatments you have had for your condition for example, freezing or surgery.

Other Medical Conditions
The safety and efficacy of APO-IMIQUIMOD cream in immunosuppressed patients has not been established. Tell your doctor about any other medical conditions that you may have before using APO-IMIQUIMOD cream, such as pre-existing auto-immune conditions.

6. How do I use APO-IMIQUIMOD cream?

Put APO-IMIQUIMOD cream on before you go to sleep for the night.

Do not put bandages or wraps or covers on top of the cream.

Only use APO-IMIQUIMOD cream as instructed by your doctor.

Step 1: Wash your hands.

Step 2: Wash the area where you are going to put the cream with mild soap and water.

Step 3: Dry the area well.

Step 4: Open the packet.

Step 5: Squeeze APO-IMIQUIMOD cream onto your fingertip.

Step 6: Put a thin layer of cream on the area shown to you by your doctor or the nurse.

Step 7: Rub a thin layer of cream in until you cannot see it.

Step 8: Throw away the opened packet.

Step 9: Wash your hands with soap and water.

Step 10: a) For external genital/perianal warts, leave the cream on for 6 to 10 hours.
b) For superficial basal cell carcinoma or actinic keratosis, leave the cream on for approximately 8 hours.
Do not shower or bathe during this time.

Step 11: a) For external genital/perianal warts, after 6 to 10 hours wash the area where the cream was applied with mild soap and water.
b) For superficial basal cell carcinoma or actinic keratosis, after 8 hours wash the area where the cream was applied with mild soap and water.

- Sufficient cream should be applied to cover the treatment area, including one centimetre of skin surrounding the tumour, for superficial basal cell carcinoma. One-sixth of a packet can treat a tumour with a maximum diameter of 2.0 cm, for superficial basal cell carcinoma.

- One packet can treat a maximum area of 25 cm^2, for actinic keratosis.

- One packet can treat a maximum area of 20 cm^2, for external genital/perianal warts.

7. When should I use APO-IMIQUIMOD cream?

Superficial Basal Cell Carcinoma (sBCC)
- Use APO-IMIQUIMOD cream 5 times per week for a maximum or 6 weeks, or as directed by your doctor.

- An example of a 5 times per week application schedule is:

Monday, Tuesday, Wednesday, Thursday and Friday

Actinic Keratosis (AK)
- Use APO-IMIQUIMOD cream 2 times per week for a total of 16 weeks, or as directed by your doctor.

- Examples of 2 times per week application schedules are:

Monday and Thursday
OR
Tuesday and Friday

External Genital and Perianal Warts (EGW)
- Use APO-IMIQUIMOD cream 3 times per week for a maximum of 16 weeks, or the length of time directed by your doctor (maximum of 16 weeks). Some patients clear their warts after 4 weeks of therapy; however, some may require up to 16 weeks of therapy.

- Examples of 3 times per week application schedules are:

Monday, Wednesday, Friday

OR
Tuesday, Thursday, Saturday

8. What do I do if I forget to apply APO-IMIQUIMOD cream?

If you miss a dose of APO-IMIQUIMOD cream, wait until the next night to apply it.

9. What should I be careful of when I use APO-IMIQUIMOD cream?

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

- Only use on the affected area of your skin.
- Use this cream the way your doctor showed you.
- Do not rub cream in your eyes, lips or nostrils.
  If you get cream in your eyes, wash your eyes out with abundant amounts of water.
- Don't use this cream in your vagina. 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.
- Wear a hat, long sleeves and use sunscreen if you must be out in the sun.
- Avoid natural or artificial sunlight, for example tanning salons, as much as possible.

10. What can I expect from APO-IMIQUIMOD cream?

- Results vary from person to person.
- For best results with APO-IMIQUIMOD cream, follow your doctor's instructions closely.

11. What side effects might I expect to see or feel?

Some people who use imiquimod cream see the area where the cream was applied get lighter or darker. Sometimes the change in the colour of the skin is permanent.

It is common for patients using imiquimod cream to experience local skin reactions such as redness, wearing away of the skin, flaking, dryness, itching, burning, crusting or scabbing, and swelling at the site of application or surrounding areas. This may be a sign that the cream is working. These local skin reactions may get better over time while using the cream or will go away after stopping the cream. Most skin reactions are mild to moderate. Severe skin reactions should be reported to your doctor. If you have questions regarding treatment or local skin reactions please talk to your doctor.

- While you are using the cream, your skin may look red. This is due to the drug's effects and is common in most patients.

- Some red spots might appear in the area where you are putting the cream. This is normal and not unusual.

- The way the area of skin where the warts or actinic keratosis lesions are may look red during the time you are using APO-IMIQUIMOD cream. Cover the wart area when you put the cream on.

12. What if I have a severe skin reaction?

Should a severe skin reaction occur, do not apply any more APO-IMIQUIMOD cream on your skin until you have talked to your doctor. Remove the cream by washing with mild soap and water. Treatment with APO-IMIQUIMOD cream can usually resume as directed by your doctor.

13. When should I call my doctor?

Call your doctor if the area where you are applying the cream is so sore or uncomfortable that you are not able to put the cream on the area or you cannot do your normal daily activities.

Call your doctor if flu-like symptoms (fatigue, fever, muscle and joint pain, chills) develop after beginning treatment with APO-IMIQUIMOD.

14. Are there any special things to know about the use of APO-IMIQUIMOD cream for Superficial Basal Cell Carcinoma?

- About 80% of the subjects tested in clinical trials had effective treatment.
- About 12 weeks after you finish using APO-IMIQUIMOD cream, your doctor will need to check the area that was treated to make sure that the skin cancer is gone. Superficial basal cell carcinoma can come back. The chances of it coming back are higher as time passes. It is very important to have regular follow-up visits with your doctor to check the area to make sure your skin cancer has not come back. Ask your doctor how often you should have your skin check.

15. Are there any special things to know about the use of APO-IMIQUIMOD cream for Actinic Keratosis?

Patients should be aware that new actinic keratosis lesions may develop during treatment with APO-IMIQUIMOD cream. These lesions may resolve during the treatment period. Even though initial actinic keratosis lesions may clear with treatment, new actinic keratosis lesions may develop in the future and require further treatment. APO-IMIQUIMOD cream is not a cure, since actinic keratosis is considered to be a chronic skin condition.

16. Are there any special things to know about the use of APO-IMIQUIMOD cream for External Genital/ Perianal Warts?

In most patients, warts disappear in 8 to 12 weeks. However, some patients get rid of their warts in 4 weeks and others take up to 16 weeks. Patients should be aware that new warts may develop during therapy. However, APO-IMIQUIMOD cream is not a cure, as the virus

that causes genital/perianal warts can also be present in normal looking skin. APO-IMIQUIMOD cream may not be able to clear virus infection in some of these cases.

- It is not known whether APO-IMIQUIMOD cream has any effect on transmission of the warts. For your own health and health of others, it is important to practice safer sex. Talk to your doctor about safer sex practices.

  APO-IMIQUIMOD CREAM MAY WEAKEN CONDOMS AND VAGINAL DIAPHRAGMS. AN ALTERNATE FORM OF CONTRACEPTION (BIRTH CONTROL) SHOULD BE USED WHILE USING APO-IMIQUIMOD CREAM.

- Some women who put APO-IMIQUIMOD cream at the opening of the vagina have pain or swelling. Sometimes this makes it hard to urinate (go to the washroom or toilet).

- **Uncircumcised male:** If you use the APO-IMIQUIMOD cream to treat warts under the penis' foreskin, you should pull back the foreskin and clean the area each morning.

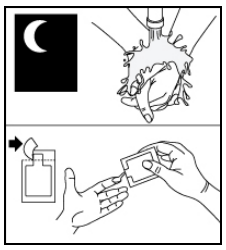
- **Sexual contact:** Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin. The effect of APO-IMIQUIMOD cream on the transmission of genital warts is unknown.

17. How should I store APO-IMIQUIMOD cream?

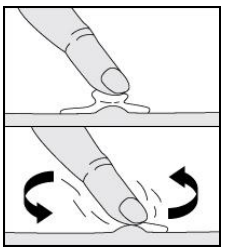
Keep out of reach of children.

Keep away from heat. Do not store near the shower or cooking area of the kitchen.

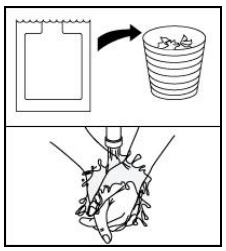
Store between 20-25°C (68°F to 77°F). Do not freeze.



1. Before going to bed, wash your hands and open a new packet. Squeeze APO-IMIQUIMOD cream onto your fingertip.

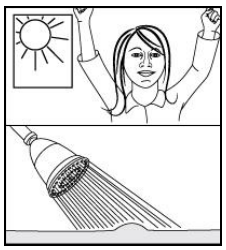


2. Apply a <u>thin</u> layer of APO-IMIQUIMOD cream onto clean, dry area and rub gently into the skin until cream vanishes.



3. After application of the cream, throw away the opened packet and wash hands with soap and water.

4. Leave APO-IMIQUIMOD cream on for the amount of time indicated by your doctor. Do not shower or bathe during this time.



5. After the right amount of time has passed, the area where APO-IMIQUIMOD cream was applied should be washed with mild soap and water.

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
    - Fax toll-free to 1-866-678-6789, or
    - Mail to:
      Canada Vigilance Program
      Health Canada
      Postal Locator 0701E
      Ottawa, Ontario
      K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at: http://www.apotex.ca/products.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last revised:

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 antitumour agent whose activity is principally due to induction of alpha interferon but other cytokines are also involved. Imiquimod induced a local immune response and a decrease in HPV-DNA for genotypes 6 and 11 in patients treating external genital/perianal warts. The immune response was characterized by significant increases in mRNA for IFN-α, 2′5′-oligoadenylate synthetase and IFN-γ in wart tissue. Although these data suggest a sequence of immunologic events initiated by imiquimod therapy, the cause of wart regression seen with imiquimod therapy has not been established.

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 percutaneus absorption, serum levels of imiquimod and metabolites were low or undetectable in these subjects.

Clinical Studies

The results of phase 1 dermal safety studies in healthy volunteers produced evidence that imiquimod cream causes irritation in healthy and to a lesser extent sun damaged skin and no

evidence that it causes photoirritation, phototoxicity, photoallergenicity or contact sensitization in healthy skin. However, phototoxicity testing was incomplete as wavelengths in the UVB range were not included and imiquimod cream has peak absorption in the UVB range (320 nm) of the light spectrum.

Superficial Basal Cell Carcinoma

In two double-blind, vehicle-controlled clinical studies, 364 patients with a biopsy confirmed primary sBCC tumours were treated with imiquimod or vehicle cream 5X/week for 6 weeks. Target tumours were to have a minimum area of 0.5 cm^2 and a maximum diameter of 2.0 cm. Tumours within 1 cm of the hairline, eyes, nose, mouth and ears, on the anogenital area or on the hands or feet, or having any atypical features were excluded. Twelve weeks after the last scheduled application of study cream, the clinical response of the target tumour was evaluated. Following the clinical assessment, the entire target tumour area was excised and examined histologically for the presence of tumour.

The primary efficacy variable was the complete response rate defined as the proportion of patients with clinical (visual) and histological clearance of the sBCC target lesion at 12 weeks post-treatment.

The study population ranged from 31 to 89 years of age (median 60 years) and 65% had Fitzpatrick skin type I or II. Data on composite clearance (defined as both clinical and histological clearance) and on histological clearance are shown in the table below.

Clearance Rates at 12 Weeks Post-Treatment for Superficial Basal Cell Carcinoma			
Study	**Endpoint**	**Imiquimod Cream**	**Vehicle Cream**
Study 1	Composite Clearance	70% (66/94)	2% (2/89)
	Histological Clearance	78% (73/94)	6% (5/89)
Study 2	Composite Clearance	80% (73/91)	1% (1/90)
	Histological Clearance	87% (79/91)	1% (1/90)
Pooled Results	Composite Clearance	75% (139/185)	2% (3/179)
	Histological Clearance	82% (152/185)	3% (6/179)

There was a statistically significant observed association between the composite clearance rate and the most intense assessment of erythema, erosion and scabbing/crusting made over the course of the study by the investigator.

One non-controlled five-year long-term follow-up study was conducted to assess the recurrence of sBCC treated with imiquimod cream applied once daily, 5 times per week, for 6 weeks. Target tumour inclusion criteria were the same as for the short-term sBCC studies described above. Efficacy assessment was done solely by clinical evaluation (i.e., no histological assessment). At 12 weeks post-treatment, patients were assessed for evidence of persistent sBCC. Subjects with no clinical evidence of sBCC entered the long-term follow-up period. The initial 12 week post-treatment clearance rate was 90% (163/182) and 162 subjects entered the long-term follow-up period for up to 5 years.

As of the 60-month visit of the follow-up period, a total of 18 subjects have had clinical evidence of sBCC recurrence at the target tumour site. For the 162 subjects who achieved initial clearance

and entered the follow-up period, the estimated non-recurrence rate at Month 60 was 87% by life table method. The highest incidence of recurrences was seen during the first 12 months of long-term follow-up with the rate of recurrences decreasing in subsequent years. For all treated patients (N=182), the estimate of achieving initial clearance and remaining clear over the duration of the 5 year follow-up period was 78%.

Estimated Clinical Clearance Rates for Superficial Basal Cell Carcinoma				
Follow-Up Period				
Follow-Up Visit after 12-Week Post-Treatment Assessment	**No. of Subjects Who Remained Clinically Clear**	**No. of Subjects with sBCC Recurrence**	**No. of Subjects Who Discontinued at this Visit with No sBCC[a]**	**Estimated Rate of Patients Who Clinically Cleared and Remained Clear[b] (N=182)**
Month 3	153	6	5	87%
Month 6	149	4	0	85%
Month 12	143	2	4	84%
Month 24	138	4	1	82%
Month 36	136	0	2	82%
Month 48	127	2	7	80%
Month 60	125	2	--	78%

[a] Reasons for discontinuation included death, non-compliance, and personal reasons.

[b] Estimated rate of 182 patients who clinically cleared and remained clear was determined by multiplying the initial clearance rate at 12 weeks post-treatment (0.90) by the estimated non-recurrence rate using life table time to event analyses for those who achieved clearance during the 5 year long term follow-up beginning after the 12 week post-treatment visit.

Actinic Keratosis

In two double-blind, vehicle-controlled clinical studies, 436 patients with AK on the head were treated with imiquimod or vehicle cream 2 times per week for 16 weeks. Patients with 4 to 8 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions within a 25 cm^2 contiguous treatment area on either face or balding scalp were enrolled and randomized in a 1:1 ratio to active or vehicle treatment. On a scheduled dosing day, the study cream was applied to the entire 25 cm^2 treatment area prior to normal sleeping hours and left on for approximately 8 hours; twice weekly dosing continued for a total of 16 weeks. Eight weeks after the patient's last scheduled application of study cream, the clinical response of each patient was evaluated. The primary efficacy variable was complete clearance. Complete clearance (designated below as "clear") was defined as a count of zero AK lesions at 8 weeks post-treatment. A secondary efficacy variable was partial clearance, defined as the percentage of patients in whom 75% or more baseline AK lesions were cleared.

The study populations included patients ranging in age from 37 to 88 years (median 66 years) and 55% had Fitzpatrick skin type I or II. All imiquimod-treated patients were Caucasians. A total of 9 patients in the imiquimod treatment group and 11 in the vehicle treatment group withdrew from the post-treatment 8 week assessment phase of the two studies. Complete and partial clearance rates are shown in the table below.

Rates (100% Lesions Cleared)					
Study	**Imiquimod Cream**	**Vehicle**	**p-Value**	**Difference in Complete Clearance Rates**	**95% Confidence Interval for the Difference**
Study 3	46% (49/107)	3% (3/110)	<0.0001	43%	(33%, 53%)
Study 4	44% (48/108)	4% (4/111)	<0.0001	41%	(31%, 51%)

Partial Clearance Rates (75% or More Lesions Cleared)					
Study	**Imiquimod Cream**	**Vehicle**	**p-Value**	**Difference in Complete Clearance Rates**	**95% Confidence Interval for the Difference**
Study 3	60% (64/107)	10% (11/110)	<0.0001	50%	(39%, 61%)
Study 4	58% (63/108)	14% (15/111)	<0.0001	45%	(34%, 56%)

There was a statistically significant observed association between the complete clearance rate and the most intense assessment of erythema made over the course of the study by the investigator.

During treatment with imiquimod cream, sub-clinical AK lesions in the treatment area may appear. During the course of treatment, 48 % (103/215) of patients experienced an increase in AK lesions relative to the number present at baseline within the treatment area. Patients with an increase in AK lesions had a similar response to those with no increase in AK lesions.

Actinic keratoses may recur in patients whose lesions initially appear clinically to have completely cleared after completion of imiquimod treatment. In an observational follow-up study, the subset of subjects who experienced complete clearance of their AK lesions at the 8 week post-treatment visit in the above two randomized trials were re-evaluated 12-18 months after the post-treatment visit. A total of 104 of the original 436 patients experienced complete clearance and were thus eligible for this study: 97 of the 215 (45%) initially randomized to imiquimod and 7 of the 221 (3%) randomized to vehicle. Of these 104 eligible subjects, 57 participated in the study. During a median follow-up period of 16 months, 42.6% (23/54) of the imiquimod-treated subjects and 33.3% (1/3) of the vehicle-treated subjects had a recurrence of AK within the original treatment area (i.e., the estimated sustained clearance rate [rate of subjects who clinically cleared and remained clear] for subjects in the original two randomized trials was 26% for the imiquimod treatment group and 2% for the vehicle treatment group). In addition, one patient, who had received imiquimod 3X/week for the treatment of AK lesions in another clinical trial (not described above) and who had complete clinical clearance of lesions at the 8 week post-treatment visit, developed a squamous cell carcinoma *in situ* in the treatment area which was excised prior to re-evaluation at the 12-18 month follow-up visit.

External Genital Warts

In a double-blind placebo-controlled clinical trial, 209 otherwise healthy patients 18 years of age and older with histologically-confirmed genital/perianal warts were treated with imiquimod cream or placebo cream 3 times a week for a maximum of 16 weeks. The median baseline wart area was 69 mm^2 (range 8 to 5525 mm^2). Imiquimod cream was proven safe and effective for the treatment of genital and perianal warts (see following table). The imiquimod cream group had wart clearance rates that were significantly greater than the placebo control. The percentage of patients achieving total clearance of their genital and perianal warts was 72% for females and 33% for males. Visible reduction in wart area occurred as early as 2 weeks and the median time to total wart clearance was 10 weeks; however, some patients required 16 weeks of therapy. Significantly more imiquimod cream patients than the placebo patients achieved >50% reduction in their baseline wart area (85% versus 38% in females, and 70% versus 22% in males, respectively). Six to nineteen percent of the cleared patients experienced a recurrence of their warts during the 12-week follow-up period.

Clearance and Recurrence Rates 3X/Week - Study 5					
Patient Group	**Treatment Group**	**Total Clearance[a]**		**Recurrence Rate[b]**	
All Patients	Imiquimod Cream	50%	(54/109)	13%	(6/45)
	Placebo	11%	(11/100)	10%	(1/10)
Females	Imiquimod Cream	72%	(33/46)	19%	(5/27)
	Placebo	20%	(8/40)	14%	(1/7)
Males	Imiquimod Cream	33%	(21/63)	6%	(1/18)
	Placebo	5%	(3/60)	0%	(0/3)

[a] Intent-to-treat analysis.
[b] Patients with total clearance who had recurrence of baseline/target warts during the 12-week follow-up period.

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).

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 5% 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 imiquimod 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.

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