IMIQUIMOD- imiquimod cream
DIRECT RX

IMIQUIMOD

1.1 Actinic Keratosis

Imiquimod Cream is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults.

1.2 Superficial Basal Cell Carcinoma

Imiquimod Cream is indicated for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured.

The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment, since safety and efficacy of Imiquimod Cream have not been established for other types of basal cell carcinomas, including nodular and morpheaform (fibrosing or sclerosing) types.

1.3 External Genital Warts

Imiquimod Cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years old and older.

1.4 Limitations of Use

Imiquimod cream has been evaluated in children ages 2 to 12 years with molluscum contagiosum and these studies failed to demonstrate efficacy. [see USE IN SPECIFIC POPULATIONS (8.4)].

1.5 Unevaluated Populations

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

Imiquimod Cream should be used with caution in patients with pre-existing autoimmune conditions.

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

The application frequency for Imiquimod Cream is different for each indication. Imiquimod Cream is not for oral, ophthalmic, or intravaginal use.

2.1 Actinic Keratosis

Imiquimod Cream should be applied 2 times per week for a full 16 weeks to a defined treatment area on the face or scalp (but not both concurrently). The treatment area is defined as one contiguous area of approximately 25 cm2 (e.g., 5 cm x 5 cm) on the face (e.g. forehead or one cheek) or on the scalp. Examples of 2 times per week application schedules are Monday and Thursday, or Tuesday and Friday. Imiquimod Cream should be applied to the entire treatment area and rubbed in until the cream is no longer visible. No more than one packet of Imiquimod Cream should be applied to the contiguous treatment area at each application. Imiquimod Cream shouldbe 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. Theprescriber should demonstrate the proper application technique to maximize the benefit ofImiquimod Cream therapy.

It is recommended that patients wash their hands before and after applying Imiquimod Cream. Before applying the cream,the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly (at least 10 minutes).

Contact with the eyes, lips and nostrils should be avoided.

Local skin reactions in the treatment area are common. [see ADVERSE REACTIONS (6.1, 6.5)] 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 tomissed doses or rest periods. Response to treatment cannot be adequately assessed until resolution of local skin reactions. Lesions that do not respond to treatment should be carefully re-evaluated and management reconsidered.

Imiquimod Cream is packaged in single-use packets, with 12 or 24 packets supplied per box. Patients should be prescribed no more than 36 packets for the 16-week treatment period. Unused packets should be discarded. Partially-used packets should be discarded and not reused.

2.2 Superficial Basal Cell Carcinoma

Imiquimod Cream should be applied 5 times per week for a full 6 weeks to a biopsy-confirmed superficial basal cell carcinoma. An example of a 5 times per week application schedule is to apply Imiquimod Cream, once per day, Monday through Friday. Imiquimod 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 Imiquimod Cream therapy.

It is recommended that patients wash their hands before and after applying Imiquimod Cream. The patient should wash the treatment area with mild soap and water before applying the cream, and allow the area to dry thoroughly.

The target tumor should have a maximum diameter of 2 cm and be located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet). The treatment area should include a 1 cm margin of skin around the tumor. Sufficient cream should be applied to cover the treatment area, including 1 centimeter of skin surrounding the tumor. Imiquimod Cream should be rubbed into the treatment area until the cream is no longer visible.

TABLE 1. Amount of Imiquimod Cream to Use of SBcc

Target Tumor

Diameter

Size of Cream Droplet to be Used

(diameter)

Approximate Amount of Imiquimod 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

Contact with the eyes, lips and nostrils should be avoided.

Local skin reactions in the treatment area are common. [see ADVERSE REACTIONS (6.2, 6.5)] A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction.

Early clinical clearance cannot be adequately assessed until resolution of local skin reactions (e.g. 12 weeks post-treatment). Local skin reactions or other findings (e.g. infection) mayrequire that a patient be seen sooner than the post-treatment assessment for clinical clearance.If there is clinical evidence of persistent tumor at the post-treatment assessment for clinical clearance, a biopsy or other alternative intervention should be considered. Lesions that do not respond to therapy should be carefully re-evaluated and management reconsidered; the safety 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 determination of clinical clearance, the patient should seek a medical evaluation. [see CLINICAL STUDIES (14.2)].

Imiquimod Cream is packaged in single-use packets, with 12 or 24 packets supplied per box. Patients should be prescribed no more than 36 packets for the 6-week treatment period. Unused packets should be discarded. Partially-used packets should be discarded and not reused.

2.3 External Genital Warts

Imiquimod Cream should be applied 3 times per week to external genital/perianal warts. Imiquimod Cream treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday or Tuesday, Thursday, Saturday. Imiquimod Cream should be applied prior to normal sleeping hours and left on the skin for 6 -10 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 Imiquimod Cream therapy.

It is recommended that patients wash their hands before and after applying Imiquimod Cream.

A thin layer of Imiquimod Cream should be applied to the wart area and rubbed in until the cream is no longer visible. 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.

Local skin reactions at the treatment site are common.[seeADVERSE REACTIONS(6.3, 6.5)]. A rest period of several days may be taken 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.

Imiquimod Cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm2; use of excessive amounts of cream should be avoided.

Imiquimod Cream, 5%, is supplied in single-use packets each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. Imiquimod Cream is supplied in boxes of 12 or 24 packets each.

None.

5.1 Local Inflammatory Reactions

Intense local inflammatory reactions including skin weeping or erosion can occur after a few applications of Imiquimod Cream and may require an interruption of dosing. [see

DOSAGE ANDADMINISTRATION(2) and ADVERSE REACTIONS (6)]. Imiquimod 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. Dosing should be interrupted or discontinued for severe vulvar swelling.

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

5.2 Systemic Reactions

Flu-like signs and symptoms may accompany, or even precede, local inflammatory reactions and may include malaise, fever, nausea, myalgias and rigors. An interruption of dosing should be considered.

[SEE ADVERSE REACTIONS (6)]

5.3 Ultraviolet Light Exposure

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 (e.g., a 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.

Imiquimod Cream shortened the time to skin tumor formation in an animal photo-cocarcinogenecity study [see NONCLINICAL TOXICOLOGY (13.1)]. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure.

5.4 Unevaluated Uses: Actinic Keratosis

Safety and efficacy have not been established for Imiquimod Cream in the treatment of actinic keratosis with repeated use, i.e. more than one treatment course, in the same area.

The safety of Imiquimod Cream applied to areas of skin greater than 25 cm2 (e.g. 5 cm X 5 cm) or the treatment of actinic keratosis has not been established [see CLINICAL PHARMACOLOGY (12.3)].

5.5 Unevaluated Uses: Superficial Basal Cell Carcinoma

The safety and efficacy of Imiquimod Cream have not been established for other types of basal cell carcinomas (BCC), including nodular and morpheaform (fibrosing or sclerosing) types. Imiquimod Cream is not recommended for treatment of BCC subtypes other than thesuperficial variant (i.e., sBCC). Patients with sBCC treated with Imiquimod Cream should have regular follow-up of the treatment site. [see CLINICAL STUDIES (14.2)].

The safety and efficacy of treating sBCC lesions on the face, head and anogenital area have not been established.

5.6 Unevaluated Uses: External Genital Warts

Imiquimod Cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience: Actinic Keratosis

The data described below reflect exposure to imiquimod cream or vehicle in 436 subjects enrolled in two double-blind, vehicle-controlled studies. Subjects applied imiquimod cream or vehicle to a 25 cm2 contiguous treatment area on the face or scalp 2 times per week for 16 weeks.

Table 2: Selected Adverse Reactions Occurring in > 1% of Imiquimod-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Actinic Keratosis)

Preferred Term

Imiquimod Cream

(n= 215)

Vehicle

(n= 221)

Application Site Reaction

71 (33%)
32 (14%)
Upper Resp Tract Infection
33 (15%)
27 (12%)
Sinusitis
16 (7%)
14 (6%)
Headache
11 (5%)
7 (3%)
Carcinoma Squamous
8 (4%)
5 (2%)
Diarrhea
6 (3%)
2 (1%)
Eczema
4 (2%)
3 (1%)
Back Pain
3 (1%)
2 (1%)
Fatigue
3 (1%)
2 (1%)
Fibrillation Atrial
3 (1%)
2 (1%)
Infection Viral
3 (1%)
2 (1%)
Dizziness
3 (1%)
1 (<1%)
Vomiting
3 (1%)

1 (<1%)

Urinary Tract Infection

3 (1%)

1 (<1%)

Fever

3 (1%)

0 (0%)

Rigors

3 (1%)

0 (0%)

Alopecia

3 (1%)

0 (0%)

Table 3: Application Site Reactions Reported by > 1% of Imiquimod-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Actinic Keratosis)

Included Term

Imiquimod Cream

(n= 215)

Vehicle

(n= 221)

Itching

44 (20%)

17 (8%)

Burning

13 (6%)

4 (2%)

Bleeding

7 (3%)

1 (<1%)

Stinging

6 (3%)

2 (1%)

Pain

6 (3%)

2 (1%)

Induration

5 (2%)

3 (1%)

Tenderness

4 (2%)

3 (1%)

Irritation

4 (2%)

0 (0%)

Local skin reactions were collected independently of the adverse reaction "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen. The most frequently reported local skin reactions were erythema, flaking/scaling/dryness, and scabbing/crusting. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Table 4: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Actinic Keratosis)

Imiquimod Cream

(n=215)

Vehicle

(n=220)

All Grades*

Severe

All Grades*

Severe

Erythema

209 (97%)

38 (18%)

206 (93%)

5 (2%)

Flaking/Scaling/Dryness

199 (93%)

16 (7%)

199 (91%)

7 (3%)

Scabbing/Crusting

169 (79%)

18 (8%)

92 (42%)

4 (2%)

Edema

106 (49%)

0 (0%)

22 (10%)

0 (0%)

Erosion/Ulceration

103 (48%)

5 (2%)

20 (9%)

0 (0%)

Weeping/Exudate

45 (22%)

0 (0%)

3 (1%)

0 (0%)

Vesicles

19 (9%)

0 (0%)

2 (1%)

0 (0%)

*Mild, Moderate, or Severe

The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions. Overall, in the clinical studies, 2% (5/215) of subjects discontinued for local skin/application site reactions. Of the 215 subjects treated, 35 subjects (16%) on imiquimod cream and 3 of 220 subjects (1%) on vehicle cream had at least one rest period. Of these imiquimod cream subjects, 32 (91%) resumed therapy after a rest period.

In the AK studies, 22 of 678 (3.2%) of imiquimod-treated subjects developed treatment site infections that required a rest period off imiquimod cream and were treated with antibiotics (19 with oral and 3 with topical).

Of the 206 imiquimod subjects with both baseline and 8-week post-treatment scarring assessments, 6 (2.9%) had a greater degree of scarring scores at 8-weeks post-treatment than at baseline.

6.2 Clinical Trials Experience: Superficial Basal Cell Carcinoma

The data described below reflect exposure to imiquimod cream or vehicle in 364 subjects enrolled in two double-blind, vehicle-controlled studies. Subjects applied imiquimod cream or vehicle 5 times per week for 6 weeks. The incidence of adverse reactions reported by > 1% of subjects during the studies is summarized below.

Table 5: Selected Adverse Reactions Reported by > 1% of Imiquimod-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Superficial Basal Cell Carcinoma)

Preferred Term

Imiquimod Cream

(n= 185)

N%
Vehicle
(n= 179)
N%
Application Site Reaction
52 (28%)
5 (3%)
Headache
14 (8%)
4 (2%)
Back Pain
7 (4%)
1 (<1%)
Upper Resp Tract Infection
6 (3%)
2 (1%)
Rhinitis
5 (3%)
1 (<1%)
Lymphadenopathy
5 (3%)
1 (<1%)
Fatigue
4 (2%)
2 (1%)
Sinusitis
4 (2%)
1 (<1%)
Dyspepsia
3 (2%)
2 (1%)
Coughing
3 (2%)
1 (<1%)
Fever
3 (2%)
0 (0%)

Dizziness

2 (1%)

1 (<1%)

Anxiety

2 (1%)

1 (<1%)

Pharyngitis

2 (1%)

1 (<1%)

Chest Pain

2 (1%)

0 (0%)

Nausea

2 (1%)

0 (0%)

The most frequently reported adverse reactions were local skin and application site reactions including erythema, edema, induration, erosion, flaking/scaling, scabbing/crusting, itching and burning at the application site. The incidence of application site reactions reported by > 1% of the subjects during the 6 week treatment period is summarized in the table below.

Table 6: Application Site Reactions Reported by > 1% of Imiquimod-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Superficial Basal Cell Carcinoma)

Included Term

Imiquimod Cream

n= 185

Vehicle

n= 179

Itching

30 (16%)

1 (1%)

Burning

11 (6%)

2 (1%)

Pain

6 (3%)

0 (0%)

Bleeding

4 (2%)

0 (0%)

Erythema

3 (2%)

0 (0%)

Papule(s)

3 (2%)

0 (0%)

Tenderness

2 (1%)

0 (0%)

Infection

2 (1%)

0 (0%)

Local skin reactions were collected independently of the adverse reaction "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Table 7: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Superficial Basal Cell Carcinoma)

Imiquimod Cream

n=184

Vehicle

n=178

All Grades*

Severe

All Grades*

Severe

Erythema

184 (100%)

57 (31%)

173 (97%)

4 (2%)

Flaking/Scaling

167 (91%)

7 (4%)

135 (76%)

0 (0%)

Induration

154 (84%)

11 (6%)

94 (53%)

0 (0%)

Scabbing/Crusting

152 (83%)

35 (19%)

61 (34%)

0 (0%)

Edema

143 (78%)

13 (7%)

64 (36%)

0 (0%)

Erosion

122 (66%)

23 (13%)

25 (14%)

0 (0%)

Ulceration

73 (40%)

11 (6%)

6 (3%)

0 (0%)

Vesicles

57 (31%)

3 (2%)

4 (2%)

0 (0%)

*Mild, Moderate, or Severe

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 subjects received rest periods. The average number of doses not received per subject due to rest periods was 7 doses with a range of 2 to 22 doses; 79% of subjects (15/19) resumed therapy after a rest period. Overall, in the clinical studies, 2% (4/185) of subjects discontinued for local skin/application site reactions.

In the sBCC studies, 17 of 1266 (1.3%) imiquimod treated subjects developed treatment site infections that required a rest period and treatment with antibiotics.

6.3 Clinical Trials Experience: External Genital Warts

In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local

skin and application site reactions.

Some subjects also reported systemic reactions. Overall, 1.2% (4/327) of the subjects 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.

Table 8: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (External Genital Warts)

Imiquimod Cream

Vehicle

Females

n=114

Males

n=156

Females

n=99

Males

n=157

All Grades*

Severe

All Grades*

Severe

All Grades*

Severe

All Grades*

Severe

Erythema

74(65%)

4 (4%)

90(58%)

6(4%)

21(21%)

0(0%)

34(22%)

0(0%)

Erosion

35(31%)

1 (1%)

47(30%)

2(1%)

8(8%)
0(0%)
10(6%)
0(0%)
Excoriation/
Flaking
21(18%)
0(0%)
40(26%)
1(1%)
8(8%)
0(0%)
12(8%)
0(0%)
Edema
20(18%)
1(1%)
19(12%)
0(0%)
5(5%)
0(0%)
1(1%)
0(0%)
Scabbing
4(4%)
0(0%)
20(13%)
0(0%)
0(0%)
0(0%)
4(3%)
0(0%)
Induration
6(5%)
0(0%)
11(7%)

0(0%)

2(2%)

0(0%)

3(2%)

0(0%)

Ulceration

9(8%)

3(3%)

7(4%)

0(0%)

1(1%)

0(0%)

1(1%)

0(0%)

Vesicles

3(3%)

0(0%)

3(2%)

0(0%)

0(0%)

0(0%)

0(0%)

0(0%)

*Mild, Moderate, or Severe

Remote site skin reactions were also reported. 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%).

Selected adverse reactions judged to be probably or possibly related to imiquimod cream are listed below.

Table 9: Selected Treatment Related Reactions (External Genital Warts)

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
38(32%)
21(20%)
34(22%)
16(10%)
Burning
30(26%)
12(12%)
14(9%)
8(5%)
Pain
9(8%)
2(2%)
3(2%)
1(1%)
Soreness
3(3%)
0(0%)
0(0%)
1(1%)
Fungal Infection*
13(11%)
3(3%)
3(2%)
1(1%)
Systemic Reactions:
Headache
5(4%)
3(3%)
8(5%)
3(2%)

Influenza-like symptoms

4(3%)

2(2%)

2(1%)

0(0%)

Myalgia

1(1%)

0(0%)

2(1%)

1(1%)

*Incidences reported without regard to causality with imiquimod cream.

Adverse reactions judged to be possibly or probably related to imiquimod cream and reported by more than 1% of subjects included:

Application Site Disorders: 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

6.4 Clinical Trials Experience: Dermal Safety Studies

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 [see ADVERSE REACTIONS (6)].

6.5 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of imiquimod cream. 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 Infestation: 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, dysuria, urinary retention

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

Vascular: Henoch-Schonlein purpura syndrome

8.1 Pregnancy

Pregnancy Category C:

Note: The Maximum Recommended Human Dose (MRHD) was set at 2 packets per treatment of Imiquimod Cream (25 mg imiquimod) for the animal multiple of human exposure ratios presented in this label. If higher doses than 2 packets of imiquimod cream are used clinically, then the animal multiple of human exposure would be reduced for that dose. A non-proportional increase in systemic exposure with increased dose of imiquimod cream was noted in the clinical pharmacokinetic study conducted in actinic keratosis subjects [see CLINICAL PHARMACOLOGY (12.3)]. The AUC after topical application of 6 packets of imiquimod cream was 8 fold greater than the AUC after topical application of 2 packets of imiquimod cream in actinic keratosis subjects. Therefore, if a dose of 6 packets per treatment of imiquimod cream was topically administered to an individual, then the animal multiple of human exposure would be either 1/3 of the value provided in the label (based on body surface area comparisons) or 1/8 of the value provided in the label (based on AUC comparisons). The animal multiples of human exposure calculations were based on weekly dose comparisons for the carcinogenicity studies described in this label. The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5, and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (577X MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (98X MRHD based on AUC comparisons).

Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407X MRHD based on AUC comparisons).

A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (87X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (87X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (41X MRHD based on AUC comparisons).

There are no adequate and well-controlled studies in pregnant women. Imiquimod Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether imiquimod is excreted in human milk following use of Imiquimod Cream. Because many drugs are excreted in human milk, caution should be exercised when Imiquimod Cream is administered to nursing women.

8.4 Pediatric Use

AK and sBCC are not conditions generally seen within the pediatric population. The safety and efficacy of Imiquimod Cream for AK or sBCC in patients less than 18 years of age have not been established.

Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established.

Imiquimod cream was evaluated in two randomized, vehicle-controlled, double-blind trials involving 702 pediatric subjects with molluscum contagiosum (MC) (470 exposed to imiquimod; median age 5 years, range 2-12 years). Subjects applied imiquimod cream or vehicle 3 times weekly for up to 16 weeks. Complete clearance (no MC lesions) was assessed at Week 18. In Study 1, the complete clearance rate was 24% (52/217) in the imiquimod cream group compared with 26% (28/106) in the vehicle group. In Study 2, the clearance rates were 24% (60/253) in the imiquimod cream group compared with 28% (35/126) in the vehicle group. These studies failed to demonstrate efficacy.

Similar to the studies conducted in adults, the most frequently reported adverse reaction from 2 studies in children with molluscum contagiosum was application site reaction. Adverse events which occurred more frequently in Imiquimod-treated subjects compared with vehicle-treated subjects generally resembled those seen in studies in indications approved for adults and also included otitis media (5% imiquimod vs. 3% vehicle) and conjunctivitis (3% imiquimod vs. 2% vehicle).

Erythema was the most frequently reported local skin reaction. Severe local skin reactions reported by treated subjects in the pediatric studies included erythema (28%), edema (8%), scabbing/crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/exudate (2%).

Systemic absorption of imiquimod across the affected skin of 22 subjects aged 2 to 12 years with extensive MC involving at least 10% of the total body surface area was observed after single and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined the dose applied, either 1, 2 or 3 packets per dose, based on the size of the treatment area and the subject’s weight. The overall median peak serum drug concentrations at the end of week 4 was between 0.26 and 1.06 ng/mL except in a 2-year old female who was administered 2 packets of study drug per dose, had a Cmax of 9.66 ng/mL after multiple dosing. Children aged 2-5 years received doses of 12.5 mg (one packet) or 25 mg (two packets) of imiquimod and had median multiple-dose peak serum drug levels of approximately 0.2 or 0.5 ng/mL, respectively. Children aged 6-12 years received doses of 12.5 mg, 25 mg, or 37.5 mg (three packets) and had median multiple dose serum drug levels of approximately 0.1, 0.15, or 0.3 ng/mL, respectively. Among the 20 subjects with evaluable laboratory assessments, the median WBC count decreased by 1.4 x 109/L and the median absolute neutrophil count decreased by 1.42 x 109/L.

8.5 Geriatric Use

Of the 215 subjects treated with imiquimod cream in the AK clinical studies, 127 subjects (59%) were 65 years and older, while 60 subjects (28%) were 75 years and older. Of the 185 subjects treated with imiquimod cream in the sBCC clinical studies , 65 subjects (35%) were 65 years and older, while 25 subjects (14%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No other clinical experience has identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Topical overdosing of Imiquimod 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 (equivalent to imiquimod content of >16 packets) was hypotension, which resolved following oral or intravenous fluid administration.

Imiquimod Cream, 5% is an immune response modifier for topical administration. Each gram contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of benzyl alcohol, cetyl alcohol, glycerin, methylparaben, oleic acid, oleyl alcohol, polysorbate 60, propylparaben, purified water, stearyl alcohol, sorbitan monostearate, white petrolatum, and xanthan gum.

Chemically, imiquimod is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of C14H16N4 and a molecular weight of 240.3. Its structural formula is:

[Image 11]

12.1 Mechanism of Action

The mechanism of action of Imiquimod Cream in treating AK and sBCC lesions is unknown.

12.2 Pharmacodynamics

Actinic Keratosis

In a study of 18 subjects with AK comparing imiquimod cream to vehicle, increases from baseline in week 2 biomarker levels were reported for CD3, CD4, CD8, CD11c, and CD68 for imiquimod cream treated subjects; however, the clinical relevance of these findings is unknown.

Superficial Basal Cell Carcinoma

An open label study in six subjects with sBCC suggests that treatment with imiquimod cream may increase the infiltration of lymphocytes, dendritic cells, and macrophages into the tumor lesion; however, the clinical significance of these findings is unknown.

External Genital Warts

Imiquimod has no direct antiviral activity in cell culture. A study in 22 subjects with genital/perianal warts comparing imiquimod cream and vehicle shows that imiquimod cream induces mRNA encoding cytokines including interferon-□ 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.

12.3 Pharmacokinetics

Systemic absorption of imiquimod across the affected skin of 58 subjects with AK was observed with a dosing frequency of 3 applications per week for 16 weeks. Mean peak serum drug concentrations at the end of week 16 were approximately 0.1, 0.2, and 3.5 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.

Table 10: Mean Serum Imiquimod Concentration in Adults Following

Administration of the Last Topical Dose During Week 16

(Actinic Keratosis)

Amount of Imiquimod Cream applied

Mean peak serum imiquimod

Concentration [Cmax]

12.5 mg (1 packet)

0.1 ng/mL

25 mg (2 packets)

0.2 ng/mL

75 mg (6 packets)

3.5 ng/mL

The application surface area was not controlled when more than one packet was used. Dose proportionality was not observed. However it appears that systemic exposure may be more dependent on surface area of application than amount of applied dose. The apparent half-life was approximately 10 times greater with topical dosing than the 2 hour apparent half-life seen following subcutaneous dosing, suggesting prolonged retention of drug in the skin. Mean urinary recoveries of imiquimod and metabolites combined were 0.08 and 0.15% of the applied dose in the group using 75 mg (6 packets) for males and females, respectively following 3 applications per week for 16 weeks.

Systemic absorption of imiquimod was observed across the affected skin of 12 subjects with genital/perianal warts, with an average dose of 4.6 mg. Mean peak drug concentration of approximately 0.4 ng/mL was seen during the study. Mean urinary recoveries of imiquimod and metabolites combined over the whole course of treatment, expressed as percent of the estimated applied dose, were 0.11 and 2.41% in the males and females, respectively.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral (gavage) rat carcinogenicity study, imiquimod was administered to Wistar rats on a 2X/week (up to 6 mg/kg/day) or daily (3 mg/kg/day) dosing schedule for 24 months. No treatment related tumors were noted in the oral rat carcinogenicity study up to the highest doses tested in this study of 6 mg/kg administered 2X/week in female rats (87X MRHD based on weekly AUC comparisons), 4 mg/kg administered 2X/week in male rats (75X MRHD based on weekly AUC comparisons) or 3 mg/kg administered 7X/week to male and female rats (153X MRHD based on weekly AUC comparisons).

In a dermal mouse carcinogenicity study, imiquimod cream (up to 5 mg/kg/application imiquimod or 0.3% imiquimod cream) was applied to the backs of mice 3X/week for 24 months. A statistically significant increase in the incidence of liver adenomas and carcinomas was noted in high dose male mice compared to control male mice (251X MRHD based on weekly AUC comparisons). An increased number of skin papillomas was observed in vehicle cream control group animals at the treated site only. The quantitative composition of the vehicle cream used in the dermal mouse carcinogenicity study is the same as the vehicle cream used for imiquimod cream, minus the active moiety (imiquimod).

In a 52-week dermal photo-cocarcinogenecity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing (3X/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with the imiquimod cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, imiquimod, to the vehicle cream.

Imiquimod revealed no evidence of mutagenic or clastogenic potential based on the results of five in vitro genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, human lymphocyte chromosome aberration assay and SHE cell transformation assay) and three in vivo genotoxicity tests (rat and hamster bone marrow cytogenetics assay and a mouse dominant lethal test).

Daily oral administration of imiquimod to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 87X MRHD based on AUC comparisons.

14.1 Actinic Keratosis

In two double-blind, vehicle-controlled clinical studies, 436 subjects with AK were randomized to treatment with either imiquimod cream or vehicle cream 2 times per week for 16 weeks. The studies enrolled subjects with 4 to 8 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions within a 25 cm2 contiguous treatment area on either the face or scalp. The 25 cm2

contiguous treatment area could be of any dimensions e.g., 5 cm x 5 cm, 3 cm by 8.3 cm, 2 cm by 12.5 cm. Study subjects ranged from 37 to 88 years of age (median 66 years) and 55% had Fitzpatrick skin type I or II. All imiquimod-treated subjects were Caucasians.

On a scheduled dosing day, the study cream was applied to the entire treatment area prior to normal sleeping hours and left on for approximately 8 hours. Twice weekly dosing was continued for a total of 16 weeks. The clinical response of each subject was evaluated 8 weeks after the last scheduled application of study cream. Efficacy was assessed by the complete clearance rate, defined as the proportion of subjects at the 8-week post-treatment visit with no (zero) clinically visible AK lesions in the treatment area. Complete clearance included clearance of all baseline lesions, as well as any new or sub-clinical AK lesions which appeared during therapy.

Complete and partial clearance rates are shown in the table below. The partial clearance rate was defined as the percentage of subjects in whom 75% or more baseline AK lesions were cleared.

Table 11: Clearance Rates (AK)

Complete Clearance Rates (100% AK Lesions Cleared)

Study

Imiquimod Cream

Vehicle

Study

46% (49/107)

3% (3/110)

AK1

Study

44% (48/108)

4% (4/111)

AK2

Partial and Complete Clearance Rates

(75% or More Baseline AK Lesions Cleared)

Study

Imiquimod Cream

Vehicle

Study

60% (64/107)

10% (11/110)

AK1

Study

58% (63/108)

14% (15/111)

AK2

Sub-clinical AK lesions may become apparent in the treatment area during treatment with imiquimod cream. During the course of treatment, 48% (103/215) of subjects experienced an increase in AK

lesions relative to the number present at baseline within the treatment area. Subjects with an increase in AK lesions had a similar response to those with no increase in AK lesions.

14.2 Superficial Basal Cell Carcinoma

In two double-blind, vehicle-controlled clinical studies, 364 subjects with primary sBCC were treated with imiquimod cream or vehicle cream 5 times per week for 6 weeks. Target tumors were biopsy-confirmed sBCC and had a minimum area of 0.5 cm2 and a maximum diameter of 2.0 cm (4.0 cm2). Target tumors were not to be located within 1.0 cm of the hairline, or on the anogenital area or on the hands or feet, or to have any atypical features. The population ranged from 31-89 years of age (median 60 years) and 65% had Fitzpatrick skin type I or II. On a scheduled dosing day, study cream was applied to the target tumor and approximately 1 cm (about 1/3 inch) beyond the target tumor prior to normal sleeping hours, and 5 times per week dosing was continued for a total of 6 weeks. The target tumor area was clinically assessed 12 weeks after the last scheduled application of study cream. The entire target tumor was then excised and examined histologically for the presence of tumor.

Efficacy was assessed by the complete response rate defined as the proportion of subjects with clinical (visual) and histological clearance of the sBCC lesion at 12 weeks post-treatment. Of imiquimod-treated subjects, 6% (11/178) who had both clinical and histological assessments post-treatment, and who appeared to be clinically clear had evidence of tumor on excision of the clinically-clear treatment area.

Data on composite clearance (defined as both clinical and histological clearance) are shown in the table below.

Table 12: Composite Clearance Rates at 12 Weeks Post-Treatment

for Superficial Basal Cell Carcinoma

Study

Imiquimod

Cream

Vehicle

Cream

Study

sBCC1

70%

(66/94)

2%

(2/89)

Study

sBCC2

80%

(73/91)

1%

(1/90)

Total

75%

(139/185)

2%

(3/179)

A separate 5-year, open-label study was conducted to assess the recurrence of sBCC treated with imiquimod cream applied once daily 5 days per week for 6 weeks. Target tumor inclusion criteria were the same as for the studies described above. At 12-weeks post-treatment, subjects were clinically evaluated for evidence of persistent sBCC (no histological assessment). Subjects with no clinical evidence of sBCC entered the long-term follow-up period. At the 12 week post-treatment assessment, 90% (163/182) of the subjects enrolled had no clinical evidence of sBCC at their target site and 162 subjects entered the long-term follow-up period for up to 5 years. Two year (24 month) follow-up data are available from this study and are presented in the table below:

Table 13: 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 sBCCa

Estimated Rate of Subjects who Clinically Cleared and remained Clearb

Month 3

153

4

5

87%

Month 6

149

4

0

85%

Month 12

143

2

4

84%

Month 24

139

4

0

79%

a Reasons for discontinuation included death, non-compliance, entry criteria violations, personal reasons, and treatment of nearby sBCC tumor.

b Estimated rate of subjects who clinically cleared and remained clear are estimated based on the time to event analysis employing the life table method beginning with the rate of clinical clearance at 12 weeks post-treatment.

14.3 External Genital Warts

In a double-blind, placebo-controlled clinical study, 209 otherwise healthy subjects 18 years of age and older with genital/perianal warts were treated with imiquimod cream or vehicle control 3 times per week for a maximum of 16 weeks. The median baseline wart area was 69 mm2 (range 8 to 5525 mm2). Subject accountability is shown in the figure below.

[Image 16]
Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.

Table 14: Complete Clearance Rates (External Genital Warts) – Study EGW1

Treatment

Subjects with

Complete

Clearance of Warts

Subjects

Without

Follow-up

Subjects with

Warts Remaining

At Week 16

Overall

Imiquimod Cream (n=109)

54(50%)

19(17%)

36(33%)

Vehicle (n=100)

11(11%)

27(27%)

62(62%)

Females

Imiquimod Cream (n=46)

33(72%)

5(11%)

8(17%)

Vehicle (n=40)

8(20%)

13(33%)

19(48%)

Males

Imiquimod Cream (n=63)

21(33%)

14(22%)

28(44%)

Vehicle (n=60)

3(5%)

14(23%)

43(72%)

Imiquimod Cream, 5%, is supplied in single-use packets which contain 250 mg of the cream. Available as: a box of 12 packets and a box of 24 packets . Store at 4-25°C (39-77°F). Avoid freezing.

Keep out of reach of children.

17.1 General Information: All Indications

Imiquimod Cream should be used as directed by a physician. [see DOSAGE AND ADMINISTRATION (2)] Imiquimod Cream is for external use only. Contact with the eyes, lips and nostrils should be avoided. [see INDICATIONS AND USAGE (1)and DOSAGE AND ADMINISTRATION (2)] The treatment area should not be bandaged or otherwise occluded. Partially-used packets should be discarded and not reused. The prescriber should demonstrate the proper application technique to maximize the benefit of Imiquimod Cream therapy.

It is recommended that patients wash their hands before and after applying Imiquimod Cream.

17.2 Local Skin Reactions: All Indications

Patients may experience local skin reactions during treatment with Imiquimod Cream (even with normal dosing). Potential local skin reactions include erythema, edema, vesicles, erosions/ulcerations, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting. These reactions can range from mild to severe in intensity and may extend beyond the application site onto the surrounding skin. Patients may also experience application site reactions such as itching and/or burning. [SEE ADVERSE REACTIONS (6)]

Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Imiquimod Cream can be resumed after the skin reaction has subsided, as determined by the physician. Patients should contact their physician promptly if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult

Because of local skin reactions, during treatment and until healed, the treatment area is likely to appear noticeably different from normal skin. Localized hypopigmentation and hyperpigmentation have been reported following use of Imiquimod Cream. These skin color changes may be permanent in some patients.

17.3 Systemic Reactions: All Indications

Patients may experience flu-like systemic signs and symptoms during treatment with Imiquimod Cream (even with normal dosing). Systemic signs and symptoms may include malaise, fever, nausea, myalgias and rigors. [see ADVERSE REACTIONS (6)] An interruption of dosing should be considered.

17. 4 Patients Being Treated for Actinic Keratosis (AK)

Dosing is 2 times per week for a full 16 weeks, unless otherwise directed by the physician. However,

the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods. [see DOSAGE AND ADMINISTRATION (2.1)]

It is recommended that the treatment area be washed with mild soap and water 8 hours following Imiquimod Cream application.

Most patients using Imiquimod Cream for the treatment of AK experience erythema, flaking/scaling/dryness and scabbing/crusting at the application site with normal dosing. [see ADVERSE REACTIONS(6.1)]

Use of sunscreen is encouraged, and patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Imiquimod Cream. [SEE WARNINGS AND PRECAUTIONS (5.3)]

Sub-clinical AK lesions may become apparent in the treatment area during treatment and may subsequently resolve. [SEE CLINICAL STUDIES (14.1)]

17.5 Patients Being Treated for Superficial Basal Cell Carcinoma (sBCC)

Dosing is 5 times per week for a full 6 weeks, unless otherwise directed by the physician. However, the treatment period should not be extended beyond 6 weeks due to missed doses or rest periods. [SEE DOSAGE AND ADMINISTRATION (2.2)]

It is recommended that the treatment area be washed with mild soap and water 8 hours following Imiquimod Cream application. [SEE DOSAGE AND ADMINISTRATION (2.2)]

Most patients using Imiquimod Cream for the treatment of sBCC experience erythema, edema, induration, erosion, scabbing/crusting and flaking/scaling at the application site with normal dosing. [SEE ADVERSE REACTIONS (6.2)]

Use of sunscreen is encouraged, and patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Imiquimod Cream. [SEE WARNINGS AND PRECAUTIONS (5.3)]

The clinical outcome of therapy can be determined after resolution of application site reactions and/or local skin reactions.

Patients with sBCC treated with Imiquimod Cream should have regular follow-up to re-evaluate the treatment site. [SEE CLINICAL STUDIES (14.2)]

17.6 Patients Being Treated for External Genital Warts

Dosing is 3 times per week to external genital/perianal warts. Imiquimod Cream treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks.

It is recommended that the treatment area be washed with mild soap and water 6-10 hours following Imiquimod Cream application.

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

Sexual (genital, anal, oral) contact should be avoided while Imiquimod Cream is on the skin.

Application of Imiquimod 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 or inability to urinate.

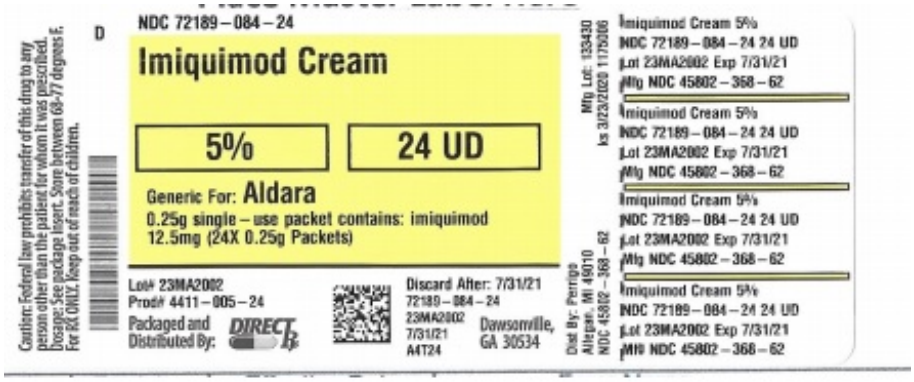
Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

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

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

Imiquimod 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.



IMIQUIMOD

imiquimod cream

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72189-084(NDC:45802-368)
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
IMIQUIMOD (UNII: P1QW714R7M) (IMIQUIMOD - UNII:P1QW714R7M)	IMIQUIMOD	12.5 mg in 0.25 g

Inactive Ingredients	
Ingredient Name	**Strength**
METHYLPARABEN (UNII: A2I8C7HI9T)	
OLEIC ACID (UNII: 2UMI9U37CP)	
WATER (UNII: 059QF0KO0R)	
PETROLATUM (UNII: 4T6H12BN9U)	
XANTHAN GUM (UNII: TTV12P4NEE)	
STEARYL ALCOHOL (UNII: 2KR89I4H1Y)	
POLYSORBATE 60 (UNII: CAL22UVI4M)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	
SORBITAN MONOSTEARATE (UNII: NVZ4I0H58X)	
CETYL ALCOHOL (UNII: 936JST6JCN)	
OLEYL ALCOHOL (UNII: 172F2WN8DV)	
GLYCERIN (UNII: PDC6A3C0OX)	
BENZYL ALCOHOL (UNII: LKG8494WBH)	

Product Characteristics			
Color	white	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-084-24	0.25 g in 1 PACKET; Type 0: Not a Combination Product	03/23/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078837	03/23/2020	

Labeler - DIRECT RX (079254320)

Registrant - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	relabel(72189-084)

Revised: 3/2020 DIRECT RX