3AI005

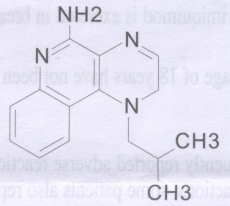
Aldara™ 樂得美™乳膏5%

Imiquimod cream, 5 %

衛署藥輸字第 023790號
本藥須由醫師處方使用

專供皮膚科外用．非眼科用藥

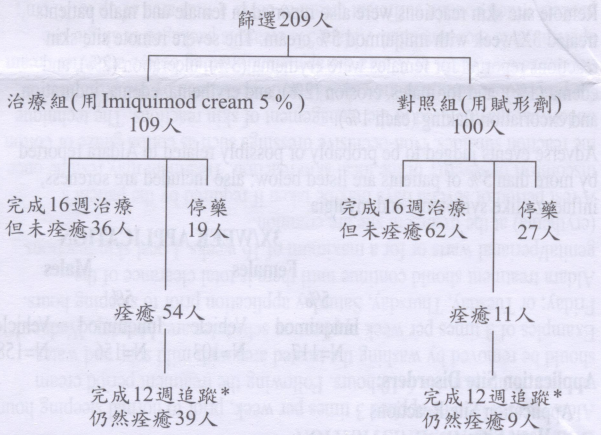
Aldara™ 是Imiquimod 註冊商標，能改善免疫反應力。每公克的5%乳膏含有50毫克Imiquimod，均勻分布於異硬脂酸、鯨臘醇、硬酯酸醇、白色凡士林、多山梨醇60、單硬酯酸山梨醇、甘油、黃嘌呤膠、純水、苯甲醇、對羥苯甲酸甲酯和對羥苯甲酸丙酯所組成灰白色、油溶水、有光澤的乳膏基劑中。
在化學結構上imiquimod是1-(2-methlpropyl)-1H-imidazo (4,5-c) quinolin-4-amine，其分子式是C14H16N6，分子量為240.3，結構式如下：



臨床藥理學：
藥效學
Imiquimod用來治療生殖器與肛門周圍疣的作用機轉迄未明瞭。在細胞培養皿上Imiquimod並無直接抗病毒作用。老鼠皮膚研究顯示Imiquimod可能會誘導細胞激素，包括α-干擾素。但是並不瞭解所發現的這些與臨床上之間的關連性。

藥動學
6位健康人身上塗上5毫克[14C] Imiquimod乳膏之後，Imiquimod 經皮膚吸收之量極少，血清中並檢測不出有放射性（少於1ng/ml 量），並且僅有＜0.9% 放射標誌劑量，是從尿與糞便排出。

臨床研究
一個以209位年齡18歲以上，患有生殖器/肛門周圍疣但健康狀況良好之病人為對象的雙盲安慰劑對照臨床試驗，給予病人Aldara™乳膏5% 或只有賦形劑軟膏，每週塗3次，最多治療16週。疣的基線面積中位數是69mm^2（範圍從8到5525 mm^2）。參與此臨床試驗病人，如下表所示：



*其他病患不是失去聯絡就是再復發

痊癒者數據如下表：疣痊癒所需的時間約10週(中數週數)。

痊癒狀況

治療組別		痊癒疣患者	無追蹤疣患者	第16週仍未痊癒疣患者
全部病人				
Imiquimod 5%	109人	50%	17%	33%
賦形劑	100人	11%	27%	62%

副作用
在臨床試驗，最常見的副作用是在患部及其周圍皮膚反應，也有一些病患有全身反應。在每週塗三次，其反應強度通常是輕微到中度的，但也有嚴重反應的報告。每天塗比每週塗三次的副作用反應較多，較強。在每週塗三次的臨床試驗中，有1.2 % (4/327)患者，因患部和周邊皮膚反應而中斷使用。

臨床試驗患部皮膚反應的發生率和輕重程度如下表:

每週塗三次之疣患部反應分析								
	輕度/中度				嚴重			
	女性		男性		女性		男性	
	5% Imiquimod	賦形劑	5% Imiquimod	賦形劑	5% Imiquimod	賦形劑	5% Imiquimod	賦形劑
病人數	114	99	158	157	114	99	156	157
紅斑	61%	21%	54%	22%	4%	0%	4%	0%
糜爛	30%	8%	29%	6%	1%	0%	1%	0%
剝皮/薄片剝落	18%	8%	25%	8%	0%	0%	1%	0%
浮腫	17%	5%	12%	1%	1%	0%	0%	0%
硬化	5%	2%	7%	2%	0%	0%	0%	0%
潰瘍	5%	1%	4%	1%	3%	0%	0%	0%
結痂	4%	0%	13%	3%	0%	0%	0%	0%
長水泡	3%	0%	2%	0%	0%	0%	0%	0%

每週塗三次Imiquimod 5% 乳膏的男女病人中也有患部外的皮膚反應，嚴重的患部外皮膚反應報告，在女性：紅斑3%、潰瘍2%、及浮腫1%；在男性有：糜爛2%、有及紅斑、浮腫、硬化、剝皮/薄片剝落各有1%。

副作用事件中經判斷認為或許或可能與Aldara™有關的報告，但超過5%者，如下表所示。其中亦包括傷口刺痛，類似感冒症狀和肌肉痛等症狀。

每週塗三次				
	女性		男性	
	5% Imiquimod	賦形劑	5% Imiquimod	賦形劑
病人數	117人	103人	156人	158人
塗抹部位障礙				
塗抹部位反應				
疣患部				
癢	32%	20%	22%	10%
燒熱	26%	12%	9%	5%
痛	8%	2%	2%	1%
傷口刺痛	3%	0%	0%	1%
黴菌感染*	11%	3%	2%	1%
全身性反應				
頭痛	4%	3%	5%	2%
類似感冒症狀	3%	2%	1%	0%
肌肉痛	1%	0%	1%	1%

*事件發生與Aldara™不一定有關係

副作用中認定或許或可能與Aldara™有關，且超過1%的報告者包括：塗抹部位障礙；疣患部反應(灼熱感、皮膚褪色、刺激、癢、痛、紅疹、敏感、傷口疼痛、刺痛與壓痛)；患部外反應 (流血、灼熱感、癢、痛、壓痛、圓癬)；全身性反應:疲累、發燒、類似感冒症狀；中樞與周邊神經系統障礙: 頭痛；胃腸系統障礙:如腹瀉；以及肌肉骨骼系統障礙:肌肉痛。

過量
人類使用Aldara™乳膏5%，因經皮膚吸收之量甚微，不會導致過量。在用兔子皮膚所做的動物試驗，皮膚塗用Imiquimod之致死劑量1600mg/m2以上。持續的塗

賦形劑	100人	11%	27%	62%

女性病人

Imiquimod 5%	46人	72%	11%	17%
賦形劑	40人	20%	33%	48%

男性病人

Imiquimod 5%	63人	33%	22%	44%
賦形劑	60人	5%	23%	72%

適應症
治療成人生殖器外部的疣、肛門周圍的疣和濕性尖疣。

禁忌
未明

警語
Aldara™乳膏並不推薦用來治療尿道的，陰道內部的，子宮頸的，直腸的，或肛門內的人類乳頭狀病毒感染。

注意事項
一般注意事項
通常有局部皮膚反應如紅斑、糜爛、剝皮/薄片剝落，及浮腫。
若是發生嚴重上述反應，要用中性肥皂和水洗掉藥品。
當上述反應情況消褪後可以再重新使用Aldara™乳膏。
目前尚無在其他皮膚藥治療生殖器疣後，緊接著使用Aldara™乳膏的臨床經驗，因此在任何先前使用藥品或開刀治療生殖器/肛門周圍疣後，傷口未癒合之前，並不推薦使用Aldara™乳膏。Aldara™有可能會加重原有的皮膚發炎。

病人使用須知
病人在使用Aldara™乳膏5% 前必須接受下列資訊和指示。
Aldara™乳膏5% 是否會減低生殖器/肛門周圍疣的傳染，目前仍未知。
Aldara™乳膏5% 可能減弱保險套和陰道隔膜的功能，因此不推薦一起使用。

1. 本藥為外用藥需由醫生指示使用，藥品不得碰觸眼睛。
2. 治療的患部不能用繃帶包紮，或覆蓋紗布。
3. 當塗上藥後，要避免做性接觸（性交，肛交，口交）。
4. 塗藥後6-10小時後用中性皂和清水洗淨。
5. 通常在塗藥區域或其周圍，有下列皮膚反應：如紅斑、糜爛、剝皮/薄片剝落，及浮腫。反應大都是輕微或中度的，若是嚴重反應，請速告知診療醫生。
6. 未割包皮之男性使用Aldara™乳膏治療包皮下之疣時，應每天縮回包皮，清洗患部。
7. 因為Aldara™並不能根治疣患，病人應注意，在Aldara™治療當中仍有可能會長出新的疣。

致癌性，細胞突變性和生育傷害性
尚無對嚙齒類動物的致癌性資料。
Imiquimod對一系列八種不同機率突變分析試驗，諸如Ames，鼷鼠淋巴細胞瘤，CHO染色體變異，人類淋巴染色體變異，SHE細胞轉型，老鼠和大頰鼠的骨髓細胞生殖，和鼷鼠顯性致命試驗，都無反應。每日口服方式投予老鼠8倍人類推薦劑量（以mg/m^{2}計），歷經交配，懷孕、分娩與哺乳的繁殖過程都無害。

懷孕
懷孕安全性分級是B級：
亦即沒有適當及控制良好的孕婦試驗。
Imiquimod對老鼠或兔子的畸胎試驗，並未發現畸胎。
以高毒性劑量，即28倍人類劑量(以mg/m^{2}計)給母鼠，發現其所生之老鼠有體重減輕與骨化延遲的現象。
另外給予懷孕母鼠8倍人類劑量之Imiquimod，對其所生老鼠之成長，並無明顯的不良作用。

哺乳的母親
未知在局部塗上Imiquimod後會不會在乳汁中發現。

兒童使用
對18歲以下的安全性和有效性尚未建立。

予過量的Aldara™乳膏5%，會引起嚴重的局部皮膚反應。在多次口服200mg以上的Imiquimod劑量後，最常見的嚴重副作用是會引起低血壓，惟在口服或靜脈輸液後，即可解除。

劑量與使用方法
Aldara™乳膏5%每週塗三次，每次在睡前才塗在患部，6-10小時之後(即第二天早晨)，用中性皂和水清洗。每週三次，可定在週一、三、五,或週二、四、六的睡前塗用。使用Aldara™治療，需持續到生殖器/肛門周圍疣完全消除，或最多用16週。
在治療時常有患部皮膚反應(紅斑)。假若患部非常不舒服或發生嚴重的皮膚反應時，可以停用幾天，待皮膚反應消褪後，可再度塗用。在處理這些皮膚反應時，可使用非閉塞性的敷物，如棉紗布或穿著棉質內褲。醫生應示範，指導病人正確的塗藥方法與藥量，以得到最佳的治療效果。塗藥前後應洗手。

Aldara™乳膏5%是單次使用劑量包裝，內含量可足夠塗20cm^2, 要避免使用過量，病人要被教導塗在外部生殖器/肛門周圍疣上，薄薄一層塗在患部，抹一抹，直到看不見藥膏為止。不可緊密覆蓋患部。

包裝：
Aldara™（Imiquimod）乳膏5%，每小包是單次使用包裝，內裝250mg乳膏，每盒12小包以下。
貯存溫度不可超過25℃，亦不可冷凍。

製造廠:
3M Health Care Limited
Derby Road, Loughborough LE11 0SF, United Kingdom
藥商:
美商3M 台灣子公司
台灣明尼蘇達礦業製造股份有限公司
地址:106 台北市敦化南路二段95號6樓
電話:(02)2704-9011

XV401600251-1

Aldara™

[al dar' a]

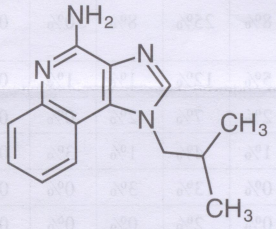
(imiquimod) Cream, 5%

For Dermatologic Use Only – Not for Ophthalmic Use.

DESCRIPTION

Aldara™ is the brand name for imiquimod which is an immune response modifier. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

Chemically, imiquimod is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3. Its structural formula is:



CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of imiquimod in treating genital/perianal warts is unknown. Imiquimod has no direct antiviral activity in cell culture. Mouse skin studies suggest that imiquimod induces cytokines including interferon-a. However, the clinical relevance of these findings is unknown.

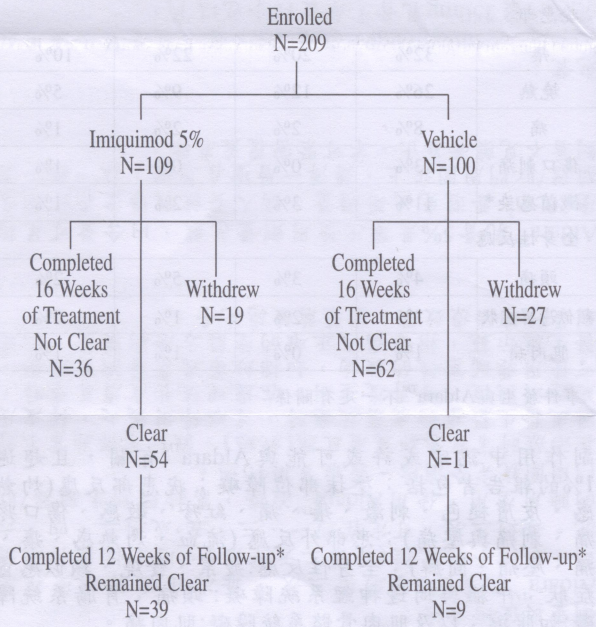
Pharmacokinetics

Percutaneous absorption of [^{14}C] imiquimod was minimal in a study involving 6 healthy subjects treated with a single topical application (5 mg) of [^{14}C] imiquimod cream formulation. No radioactivity was detected in the serum (lower limit of quantitation: 1 ng/mL) and <0.9% of the radiolabelled dose was excreted in the urine and feces following topical application.

CLINICAL STUDIES

In a double-blind, placebo-controlled clinical trial, 209 otherwise healthy patients 18 years of age and older with genital/perianal warts were treated with Aldara 5% cream or vehicle control 3X/week for a maximum of 16 weeks. The median baseline wart area was 69 mm^2 (range 8 to 5525 mm^2). Patient accountability is shown in the figure below.

1004-IMIQ – PATIENT ACCOUNTABILITY



*The other patients were either lost to follow-up or experienced recurrences.

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

CLEARANCE – STUDY 1004

Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Imiquimod was not found to be 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.

In developmental studies with offspring of pregnant rats treated with imiquimod (8 times human dose), no adverse effects were demonstrated.

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

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 3X/week application. **These reactions were more frequent and more intense with daily application than with 3X/week application.** Overall, in the 3X/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.

3X/WEEK APPLICATION
Wart Site Reaction as Assessed by Investigator

	Mild/Moderate				Severe			
	Females		Males		Females		Males	
	5% Imiquimod N=114	Vehicle N=99	5% Imiquimod N=156	Vehicle N=157	5% Imiquimod N=114	Vehicle N=99	5% Imiquimod 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 3X/week with imiquimod 5% 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 Aldara reported by more than 5% of patients are listed below; also included are soreness, influenza-like symptoms and myalgia.

3X/WEEK APPLICATION

	Females		Males	
	5% Imiquimod N=117	Vehicle N=103	5% Imiquimod 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 Aldara.

Adverse events judged to be possibly or probably related to Aldara and reported by more than 1% of patients include: **Application Site Disorders:**

CLEARANCE – STUDY 1004

Treatment	Patients With Complete Clearance of Warts	Patients Without Follow-up	Patients With Warts Remaining at Week 16
Overall			
imiquimod 5% (N=109)	50%	17%	33%
vehicle (N=100)	11%	27%	62%
Females			
imiquimod 5% (N=46)	72%	11%	17%
vehicle (N=40)	20%	33%	48%
Males			
imiquimod 5% (N=63)	33%	22%	44%
vehicle (N=60)	5%	23%	72%

INDICATIONS AND USAGE

Aldara 5% cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in adults.

CONTRAINDICATIONS

None known

WARNINGS

Aldara 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.

PRECAUTIONS

General

Local skin reactions such as erythema, erosion, excoriation/flaking, and edema are common. Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with Aldara cream can be resumed after the skin reaction has subsided. There is no clinical experience with Aldara cream therapy immediately following the treatment of genital/perianal warts with other cutaneously applied drugs; therefore, Aldara cream administration is not recommended until genital/perianal tissue is healed from any previous drug or surgical treatment. Aldara has the potential to exacerbate inflammatory conditions of the skin.

Information for Patients

Patients using Aldara 5% cream should receive the following information and instructions: The effect of Aldara 5% cream on the transmission of genital/perianal warts is unknown. Aldara 5% cream may weaken condoms and vaginal diaphragms. Therefore, concurrent use is not recommended.

1. This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided.
2. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
3. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.
4. It is recommended that 6-10 hours following Aldara 5% cream application the treatment area be washed with mild soap and water.
5. 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. Severe skin reactions can occur and should be reported promptly to the prescribing physician.
6. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.
7. Patients should be aware that new warts may develop during therapy, as Aldara is not a cure.

Carcinogenicity, Mutagenesis, and Impairment of Fertility

Rodent carcinogenicity data are not available. Imiquimod was without effect in a series of eight different 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. Daily oral administration of imiquimod to rats, at doses up to 8 times the recommended human dose on a mg/m^2 basis throughout mating, gestation, parturition and lactation, demonstrated no impairment of reproduction.

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.

OVERDOSAGE

Overdosage of Aldara 5% cream in humans is unlikely due to minimal percutaneous absorption. Animal studies reveal a rabbit dermal lethal imiquimod dose of greater than 1600 mg/m^2. Persistent topical overdosing of Aldara 5% 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

Aldara 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. Aldara 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'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. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara therapy. Handwashing before and after cream application is recommended. Aldara 5% 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 should be instructed to apply Aldara cream to external genital/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.

HOW SUPPLIED

Aldara (imiquimod) cream, 5%, is supplied in single-use packets which contain 250 mg of the cream. Available as: box of 12 packets.
Do not store above 25°C. Avoid freezing.

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