ALDARA™ / Imiquimod 5%

ABSTRACT MONOGRAPH

By

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The information presented in this document is excerpted from authoritative sources compiled by the author during the course of five-years of literature research and investigation. Comments by the author are clearly identified as "commentary". All other statements are quoted verbatim from the source materials unless otherwise indicated, with emphasis added in some instances.

Full disclosures of testimony given in U. S. Federal Court actions will be made available upon formal written request.

SOURCES OF INFORMATION

3M Pharmaceuticals & 3M.com website

B. HÄGGQVIST & P. HULTMAN
Clinical & Experimental Immunology

Herbert Slade, MD
Director of 3M Pharmaceuticals
St. Paul, Minnesota

EMEA
The European Agency for the
Evaluation of Medicinal Products

Alain Rohan, MD
Director of Drug Surveillance and Information
3M Pharmaceuticals

International Agency
for Research on Cancer

Mark A. Tomai
Director of Research & Development
3M Pharmaceuticals

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Clinica Bella Medica
Department of Obstetrics & Gynecology
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3M Pharmaceuticals / S.O.S

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3M Pharmaceuticals

Gary Richwald, MD, MPH,
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D. M. Klinman
FDA – Staff

Richard Beasley vs 3M Pharmaceuticals, etal
U.S. District Court for the Eastern District of Texas
Marshall Division – Civil Action # 2-02CV-20-TJW

FDA Drug Approval Data
NDA# 20-723 Aldara/5% imiquimod

OPENING STATEMENT

This monograph is a “snap-shot” of a five year extended research program in which over 9,000 pages of documents and data were assembled on the drug Aldara/imiquimod. The research program also collected information and documentation relating to 3M Pharmaceuticals, the manufacturer of Aldara.

Since obviously it is impractical to include in this abstract monograph reviews on each and every important topic of my research, this “snap-shot” collection of data should be considered a representative example that demonstrates the significance of the total collection of data.

In the near future, there will be a release of at least three more of these abstract monographs each covering new and additional topics until all subject matter from my research has been discussed and documented.

Additional support documents will be made available upon formal written request.

SUBJECT MATTER ADDRESSED IN THIS MONOGRAPH

The data clearly demonstrates the drug Aldara/imiquimod as one lacking almost any attributes for safe pharmacological controls, and for certain lacks all clinical predictability while stimulating the immune systems and other physiological mechanisms within the host users body.

The data also reflects a drug with not only a questionable safety profile but also clearly demonstrates an alarming uncertainty of its safe use as a “patient applied” highly potent immune altering treatment in the consumer population.

The data describes Aldara as a topical chemotherapy with the capability of stimulating immune activity to induce “unknown levels”, but certainly higher than innate baseline respective levels, for each of a large family of cytokines and other materials related to the immune system. Upon breach of the epidermis, which regularly occurs during most treatments, the users treatment converts to **systemic multi-cytokine chemotherapy.** This entire large family of drug induced cytokine activity then becomes a “direct and undesirable” gross systemic multi-cytokine chemotherapy treatment in the users body “in the absence of any targeted infection or antigen”. This action coupled with absorption of each element of the vehicle found in Aldara are then all made readily available for transparent delivery into blood circulation via the “subcutaneous” open ulcerated lesion created by consistent dosing, not overdosing as 3M proclaims, of the treatment target site. **Again, self applied or patient applied use of Aldara must be reconsidered.**

3M publicized data has historically described Aldara as a drug with almost no ability to release its “single active agent” imiquimod into blood circulation through the route of percutaneous absorption. 3M as well as many independent researchers including the FDA have all characterized the percutaneous absorption of imiquimod, should it occur, as an event that could yield catastrophic consequences for the user. Yet the data, along with 3M Federal Testimony, has systematically demonstrated not only that imiquimod reaches circulation but how it is accomplished and reveals actual cases and resulting consequences of such to the injured host user immune system and bodily physiological functions as a whole.

Percutaneous absorption of imiquimod is a common occurrence during treatments using Aldara. Data also demonstrates that systemic side-effects can only originate from two sources, both of which are derived from “percutaneous absorption”. They are (1) absorption into circulation cytokines induced at the treatment site itself and within the epidermis and (2) direct absorption of the imiquimod molecule out of the vehicle into circulation via the blood enriched lesion created by the erosion and breach of the epidermis which develops into subcutaneous delivery of the drug. Or, a combination of both (1) and (2). (Imiquimod in whole blood is many times more potent at inducing the full list of cytokines in circulation than it is when applied to intact skin.)

Aldara and the components of its vehicle are designed to quickly and efficiently release imiquimod molecules from the vehicle into the contact surfaces of the skin and membrane tissues. 3M has testified that by placing Aldara in open ulcerated lesions, typically seen in most treatments, imiquimod molecules would be expected to absorb and thus enter circulation at greater ease and higher rates than is the case of topical intact skin applications alone.

The data describes how imiquimod is capable of stimulating normal immune systems to “break tolerance” resulting in autoimmunity. Other long term and permanent injuries were sited which are serious but unrelated to autoimmunity.

A poll of university level medical professors was taken in which potential commercial biases were removed in an effort to retain as much integrity as possible in the results. Originally, the poll consisted of questions on the drug Aldara and called for their responses based upon the commercial name of the drug as the subject identifier. The answers were consistent with the publicized data or primarily “positive” in nature. Suspecting bias in their responses, I realized the questions in the poll could be framed without the possibility for this “commercial” bias by simply referring to the entire family of induced cytokines which is the “only” drug action for Aldara/imiquimod and leave off any mention of the commercial ties with 3M or to any specific drug that might lead to bias in responses. As the poll data reflects, a much different picture for Aldara quickly emerged from the research community depicting a more truthful and very dangerous profile for Aldara.

INTRODUCTION

COMMENTARY

Aldara™ is the brand name for imiquimod (**IQ**), and is a member of the chemical class known as *imidazoquinoline amine*. **Aldara**™ is manufactured by 3M Health Care Limited and distributed to over 100 countries throughout the world by other 3M affiliates. **Aldara**™ was approved through the *FDA Fast-Track Approval Process* in February of 1997 for treatment of genital warts or HPV. Since that time, the FDA has approved its use in treatments of AK pre-cancerous lesions and sBCC superficial basal cell carcinoma skin cancers. Other indications for **IQ** are presently under investigations. Prior attempts made at discovering more indications for **IQ** have largely failed.

The *imidazoquinoline amine* (**IQ**) class of compounds was first reported synthesized in 1980. In the mid-1980's, researchers discovered **IQ** to be implicated in a number of carcinogenic biological activities and launched numerous investigations into this suspicious activity.

Below are excerpts from their findings:

International Agency for Research on Cancer

***IQ** is reasonably anticipated to be a human carcinogen based on sufficient evidence of benign and malignant tumor formation at multiple tissue sites in multiple species of experimental animals (IARC 1993).*

*Studies have uniformly shown that **IQ** is genotoxic in a wide variety of bacterial, plant, and mammalian test systems, mainly with metabolic activation, and in animals in vivo (IARC 1993). **IQ** induces DNA and chromosomal damage in various cultured human cells, including mutations, chromosomal aberrations, sister chromatid exchange, micronuclei, and unscheduled DNA synthesis. **IQ** is metabolized to reactive intermediates via acetylation and hydroxylation.*

*No available data suggest that mechanisms thought to account for **IQ's** induction of tumors in experimental animals would not also operate in humans.*

Full Text Report Attached: (page 26)

CARDIAC DAMAGE INDUCED BY IQ IN NONHUMAN PRIMATES

By:
The National Cancer Institute, Bethesda, Md.
Armed Forces Institute of Pathology, Washington, DC.

*"These findings suggest that chronic exposure to **IQ** can lead to myocardial damage in monkeys."*

Commentary

IQ is an *immune response modifier* drug that uniquely alters the mechanics of the host users immune system by enhancing the production of a number of cytokines within the immune system some of which un-naturally co-exists at the same time during an IQ altered immune response. The following is a list of those cytokines.

CYTOKINES INDUCED BY IMIQUIMOD

Reference: IMIQUIMOD
by: Gary A. Richwald

INF-a / g, TNF-a, IL-1, IL-1Ra, IL-6, IL-8, IL-10, IL-12 p40,

G-CSF, GM-CSF, 1-a(MIP-1), MIP-1b, and MCP-1

*These cytokines, including several subtypes of each, are all induced within PBMC of the host upon each exposure to **IQ**.*

DEFINITION:

Cytokines are chemical messengers that control immune responses.

Commentary

Cytokines are very important elements of a well functioning immune system. Only when production of cytokines are naturally regulated by intact immune

systems are we allowed the enjoyment of good health. Loss of or significant interference with natural regulation of cytokine production is therefore responsible for the initiation and sustainment of some of the most dreaded diseases known to mankind.

As the data reflects, IQ profoundly disturbs and alters the natural regulation and timing of production between these cytokines thus the timing in which each are induced to become part of an immune response. IQ forces activation of some cytokines to be un-naturally induced when normally they would not necessarily be found co-existing at the same time in a natural immune response; while other cytokines get suppressed. It is also worth noting that every immune system reacts very differently to IQ stimulation. Once, immune systems are stimulated by IQ there is no predictability for induced levels of each respective cytokine.

Contrary to existing cytokine injection chemotherapy, where known quantities of a specific cytokine(s) are injected into patients, IQ forces the immune system to produce this entire list of cytokines continually, uncontrollably, and are all allowed to reach totally unknown levels within each patients body. In this respect, IQ is nothing more than a form of **patient applied, gross and uncontrollable, cytokine chemotherapy.**

3M data consistently focuses on specific cytokines from the list of >13 IQ-induced cytokines as their support for the safe pharmacological actions of IQ. However, 3M cannot disregard the fact that the ***total*** list of cytokines are induced during each immune stimulation by IQ, albeit at unknown levels for each, and that in order to reach a **complete** scientific understanding of the ***true*** pharmacological actions for IQ one must consider the impact of the total list of induced cytokines being made available to the user, not a single or selective cytokine from the list that might support a *positive* position or argument of the moment.

Further, IQ users do not enjoy the high margin of safety associated with traditional cytokine injection chemotherapy regimens. Injections are measured, precisely calculated, and timely regimens of a desired and known substance. Pharmacological effects from the injections have known and predictable rates of decay in which the patient is safely subjected to known quantities and short exposures to drug activity, which is often measured in hours. In contrast, IQ users self apply the drug. In many regimens, IQ is applied up to once each day for weeks on end and directly into blood enriched lesions where 3M data states that the full list of IQ induced cytokines will be made continually available within the patient, and for up to three days following the removal of the last application. Unlike injections, the IQ user cannot remove himself/herself from the effects of this entire list of internally induced and sustained cytokine production, as is the case with injections. The following is an industry wide understanding and acceptance of the consequences found to occur when cytokine production within the immune system, for any reason, goes awry.

ASSOCIATIONS BETWEEN SINGLE CYTOKINES AND DISEASES

EACH CYTOKINE BELOW IS INDUCED BY IQ

INF-a - long term effects include damage to nerves, the spinal cord, and brain tissue, inducement of arthritis and lupus. It induces systemic flu-like symptoms.

TNF-a - is involved in the manifestations of most all autoimmune diseases and inflammatory conditions. **Anti**-TNF-a drugs are now treating these diseases.

IL-1 - data suggest that IL-1 may initiate or promote inflammation within the central nervous system. It is also implicated in initiating and sustaining autoimmunity.

IL-1Ra - regulates production of IL-1. **IQ** interferes with the safe regulation of IL-1 by IL-1ra, which can lead to spontaneous autoimmunity.

IL-6 - Deregulation of IL-6 production is implicated in the pathology of several disease processes. The expression of constitutively high levels of IL-6 in transgenic mice results in fatal plasmacytosis, which has been implicated in human multiple myeloma. Increased IL-6 levels are also observed in several diseases, including rheumatoid arthritis (RA), systemic-onset juvenile chronic arthritis (JCA), osteoporosis, and psoriasis. IL-6 is critically involved in experimentally induced autoimmune disease, such as antigen-induced arthritis (AIA), and experimental allergic encephalomyelitis. All these clinical data and animal models suggest that IL-6 plays critical roles in the pathogenesis of autoimmune diseases. Elevated levels of IL-6 may be associated with an increased risk of heart attack, and stroke.

IL-8 - is strongly stimulated by IL-1 and TNF-alpha. Elevated concentrations are observed in psoriasis rheumatoid arthritis, chronic polyarthritis, and tumor development.

GM-CSF- is a pro-inflammatory cytokine. It has been associated with breaking tolerance and inducing autoimmunity.

MISCELLANEOUS FACTS ABOUT CYTOKINES INDUCED BY IQ

Pro-inflammatory (Th1) cytokines (**IFN-g, TNF-a, IL-12**) contribute to Myelin and axonal damage.

IL-12 and **TNF-alpha** are proteins that trigger the body's immune system to fight disease but are also involved in the swelling and tissue destruction that marks autoimmune disorders.

The balance between **IL-1** and **IL-1Ra** in local tissues plays an important role in the susceptibility to and severity of many diseases.

Arthritis, Crohn's disease, ulcerative colitis and lupus erythematosis are autoimmune diseases characterized by a high level of **IL-1.**

TNF-a plays a key role in psoriatic arthritis and synovial inflammation and in joint destruction.

IL-12 in the absence of an infection **(as with IQ use)** may predispose to autoimmunity.

MICROBIOLOGIST REVIEW

FDA APPROVAL DATA FOR ALDARA
PAGE 172

"*The applicant stated that imiquimod is an immune response enhancer. It is claimed that cells of the monocyte/macrophage lineage produce and secrete several subtypes of interferon-a, tumor necrosis factor-a, interleukins – 1, 6, 8, 10, granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor and macrophage inflammatory factor –1. Evaluation of the data provided in support of the claim is equivocal with lack of the ability to distinguish between cell damage response and pharmacological response. Furthermore, the production of multiple cytokines may not be synonymous with therapeutic benefit since the cytokines exhibit pleotrophic effects* ***ranging from beneficial to detrimental consequences.***

Commentary

A non-scientific poll was conducted by the author of this *monograph* to determine how dangerous professionals, within the fields of epidemiology and rheumatology, considered this list of **IQ** induced cytokines to be for users of the drug **Aldara**™.

All respondents were senior teaching professors at various major U. S. medical universities, and were all asked to answer three questions derived from the introductory statement below.

INTRODUCTORY STATEMENT

The following cytokines **(from the list above)** *are found to be present systemically at abnormal levels in a healthy adult who is not undergoing an immune challenge (i.e., no infection or exposure to foreign antigens that would elicit an immune response). Assume that the elevated levels of the listed cytokines are above normal for that individual, but below lethal levels, consistently for a period of 21 days.*

Question- (1)

What is the most likely result or results of that exposure, if it is possible to predict a result?

Response

Wide spread autoimmune like disorders (most common answer)***, synovitis, serositis, fatigue, malaise, flu-like symptoms, fever, problems with digestive tract, back pains, headaches, vision problems, and other miscellaneous systemic wide symptoms.***

Question-(2)

Is it possible for such an exposure to overcome tolerance and lead to one or more autoimmune disorders?

Unanimous Response

(YES)

Question-(3)

On a scale of 1-10 (or as closely as you can quantify), what is the risk of permanent damage and/or immune system alteration from the exposure?

Average Response

(7)

DEFINITION:

Cytokines are chemical messengers that control immune responses. They are secreted by white blood cells, T cells, epithelial cells and some other body cells. There are at least 17 different kinds of interleuken and 3 classes of interferon called alpha, beta and gamma and various subsets. Interleukens and interferons are called "cytokines" and there are two general groupings, **Th1** and **Th2**.

Commentary

The FDA has performed extensive laboratory investigative study into agents that interfere with the delicate natural balance, which industry wide research data supports must be constantly maintained, between the **Th1** and **Th2** groups of cytokines in order to insure the safe and stable operations of our immune systems. Below is an excerpt from that study:

AUTOIMMUNITY & TOLERANCE INDUCED
BY VACCINES, HORMONES, CYTOKINES & RETROVIRUSES

authored by: D. M. Klinman - FDA

SUPPORTING AGENCIES:

U. S. Dept. of Health & Human Services; Public Health Service;
National Institute of Health

FDA STATEMENT

*"Our experiments show that agents capable of altering the balance between Th1 and Th2 cytokines profoundly impact the initiation, severity, and persistence of both systemic and organ specific **autoimmunity**."*

Commentary

The following researchers determined that by increasing the Th1 cytokines while suppressing the Th2 cytokines, **(3M stated drug mechanism for IQ)**, establishes an environment conducive for the manifestation of autoimmunity.

Effects of deviating the Th2-response in murine mercury-induced autoimmunity towards a Th1-response

B. HÄGGQVIST & P. HULTMAN

Clinical & Experimental Immunology
Volume 134 Issue 2 Page 202 - November 2003
doi:10.1046/j.1365-2249.2003.02303.x

We conclude that manipulating the cytokine status, by altering the Th1/Th2 balance, will influence autoimmune disease manifestations.

IQ ALTERS *TH1/TH2* CYTOKINE BALANCE

Commentary

The only known pharmacological drug action for **IQ** is that in which **IQ** alters this Th1/Th2 balance by increasing the levels of cytokines associated with Th1, while decreasing or suppressing the levels of those cytokines associated with Th2. Below is an excerpt from a U. S. Patent Assigned to 3M.

United States Patent #6,039,969 – March 21, 2000 – 3M inventor: Mark A. Tomai

*….imidazoquinoline amines (**IQ**) …by administering a therapeutically effective amount of such **(IQ)** compounds in order to inhibit Th2 immune response, suppress IL-4/IL-5 cytokine induction and eosinophilia, as well as enhance Th1 immune response.*

MECHANISMS UNDERLYING IMIQUIMOD-INDUCED REGRESSION OF BASAL CELL CARCINOMA IN VIVO

By: Herbert Slade, etal

*"Imiquimod induces sBCC clearance by **directly altering** the host's innate and acquired immunity, and this effect is at least local, **if not systemic."***

3M DRUG MONOGRAPH AS OF AUGUST, 2005

3M Website

PRECAUTIONS:

Aldara cream should be used with caution in patients with pre-existing autoimmune conditions.

Commentary

Although known for a decade, 3M only recently (Aug. 2005) added to their monograph for Aldara a statement, effectively warning, that IQ's enhancement of a Th1 immune response exacerbates a users existing autoimmune condition by increasing levels of the very Th1 pro-inflammatory cytokines involved with their autoimmune disease.

EXAMPLES OF IQ INDUCED INJURIES

SUCCESSFUL TREATMENT OF A HIGH-GRADE INTRAEPITHELIAL NEOPLASIA WITH IMIQUIMOD (IQ), WITH VULVAR PEMPHIGUS AS A SIDE EFFECT.

By: G. Campagne , M. Roca & A. Martinez

The posterior biopsies confirm the absence of lesions but show drug-induced pemphigus as a side effect.

IMIQUIMOD: POTENTIAL RISK OF AN IMMUNOSTIMULANT

By: E. Benson

This case highlights the potential risk of using imiquimod cream (an immunostimulant) in a patient who has a condition requiring immunosuppression, such as autoimmune disease or an organ transplant.

CHRONIC NEUROPATHIC PAIN ASSOCIATED WITH IMIQUIMOD

By: Dept. of Neurology – University of California

Two patients developed neuropathic pain after the application of imiquimod for the treatment of warts. In both cases, the skin barrier was compromised, by erosion of the glans penis and took years to resolve.

Commentary

Due to the wide physiological disparities between host's immune systems stimulated by **IQ**, induced levels for each of these respective cytokines within any given host user of the drug **IQ** is inherently unpredictable.

This induction of cytokine activity occurs with drug PBMC concentrations of between 0.5 μg/ml – 5 mg/ml.

ref: IMIQUIMOD by: Gary A. Richwald

This further demonstrates the wide variations that exist between host's immune responses to **IQ**. Cytokine induction occurs in some users at very low IQ concentrations while much larger concentrations of IQ are required in others.

3M Federal Testimony Beasley vs 3M Pharmaceuticals, etal

by: Dr. Herbert Slade / Director of 3M Pharmaceuticals

We knew that some people responded and some people didn't. We don't know why. I still don't know why. And it was the best information I could give him at the time as to what might cause one individual to have a lot of global reactions and another individual to not have a lot of global reactions, that it wasn't necessarily the amount of drug, that there were other factors.

Commentary

This statement further supports the idea that IQ only catalyzes an un-natural immune process by which "global reactions", un-related to drug quantity, but rather a response to drug and drug "induced" systemic wide activity subjects the users to unnecessarily high potential for serious injuries.

3M MONOGRAPH FOR ALDARA

August, 2005

"However, it appears that systemic exposure may be more dependent on surface area of application than amount of applied drug."

This statement tends to refute prior 3M publicized claims that systemic side effects are largely due to the excessive use and over application of Aldara to treatment sites by its users. Thin and conservative applications of Aldara to the skin, is in fact, just as likely to result in "systemic exposure" of the drug and drug action, as are gross applications.

Commentary

3M has historically taken the position that the active agent in Aldara™, IQ, will be retained and contained to the topical application site itself, and will not, and cannot be released into systemic blood circulation. Below are a few conflicting points of view on the subject of absorption:

DAILY REGIMENS INCREASE TOXICITY

FDA APPROVAL LETTER FOR ALDARA – NDA 20-723
FEBRUARY 27, 1997

Frequency of administration (for HPV):

*"The applicant has presented data evaluating the effect of **daily** imiquimod application (study 1005-IMIQ). These data do not support any substantial increase in efficacy and clearly demonstrate increased toxicity."*

ABSORPTION OF IQ INTO CIRCULATION

IMIQUIMOD

by: Gary A. Richwald

The immunological activity of imiquimod **(IQ)** *is thought to be mediated through the induction, both locally and systemically, of cytokines such as IFN and IL-12…*

..topical administration of imiquimod **(IQ)** *could potentially lead to significant systemic effects if percutaneous absorption were extensive…*

SUMMARY OF PRODUCT CHARACTERISTICS FOR ALDARA™

Ref: U. K. – EMEA/EPAR/CPMP – pre-2004

When applied topically, systemic overdosage with imiquimod cream is unlikely due to minimal percutaneous absorption.

EXTERNAL GENITAL WARTS THERAPY NOW INDICATED FOR ADOLESCENTS

By: 3M Pharmaceuticals

*In addition, clinical studies show Aldara cream has activity throughout skin tissue --- **beyond the basal layer** --- where the virus is more likely to be found.*

ALDARA PRODUCT MONOGRAPH

Ref: 3M Pharmaceuticals website 3M.com – August 2005

*Persistent topical overdosing of **Aldara**™ Cream could result in an increased incidence of severe local skin reactions and may increase the risk for **systemic reactions**.*

3M Defines "systemic reactions"

U. S. Federal Testimony – Beasley vs 3M Pharmaceuticals etal

by: 3M's Dr. Alain Rohan – Director of 3M Drug Surveillance and Information:

Question:
*Would a **systemic reaction** be indicative if the chemical* **(IQ)** *has gotten into the system somehow beyond just the area where the topical cream was applied?*

Rohan's Answer:
Yes, that's really the only scientific way you can interpret that.

Question:
And it would be indicative that it got into perhaps the bloodstream or the nervous system or some other part of the body to have this effect?

Rohan's Answer:
Yes, either that or it's excited some other production of substances or cells that then have traveled around the rest of the body.

Commentary

A high percentage of treatments will result in the application site becoming an open lesion where the epidermis has been breached well below the basal layer.

The patient will, under the instructions of the physician, continue to apply Aldara directly into this open lesion which has been created by the consistent dosing of the site, NOT OVERDOSING, that almost always creates this "severe local skin reaction" described in the above 3M product monograph statement. This in turn subjects the user to the very real possibility of drug absorption into the systemic compartment along with all the serious consequences known to occur from such.

Commentary

Vinita Polyne, a 3M/S.O.S Pharmacist stated, in the year 2000, that applying Aldara directly into an open wound was the same as administering the drug intravenously into the blood stream.

3M STATED DRUG ACTION FOR IQ

Dr. Herbert Slade – Director of 3M Pharmaceuticals
U.S. Federal Testimony

"….the **(IQ)** *drug signal to the system is quite non-specific. It doesn't have a signature, doesn't say you have a virus or you have a bacteria or even cancer. It just says you have got something that is not supposed to be there, and have a look at it, do something about it."*

Commentary
This statement sums up the overall ability of IQ to identify and target **any** cell of the body for destruction. It only follows that normal self-cells will also be caught up in this non-specific recognition process since IQ actions bypasses and retards many of the natural signaling steps and safeguards that allow the normally functioning immune system to readily distinguish between foreign and self cells, thus preventing autoimmunity from occurring.

3M'S DRUG SAFETY STATEMENT FLAWED

Commentary
During the course of developing safety statements for their drugs, pharmaceutical companies perform clinical trials on animals to determine a number of attributes for proposed indications of a drug. One such statement is termed the **L**ethal **D**ose **L**imit, which in the case of Aldara, is determined by topically applying Aldara to wide surface areas of an animals skin until the animal dies from the pharmacological effects of the exposure. This LDL statement is an indicator trained professionals use to determine how dangerous a drug may or may not be prior to prescribing its use.

For example: The **less drug** it takes to inflect death upon an animal test subject the **more potent** that drug is thus the more important the LDL statement becomes to trained professionals in determining safe regimen characteristics for their patients, or if in fact the drug should be used at all. On the other hand, the **more drug** it takes to inflect death upon the animal test subject the **less potent** the drug appears to be, thus the less important the LDL statement becomes in determining safety for patient drug therapy.

Professionals might be more inclined to prescribe a drug with a higher LDL due to its perceived higher safety feature. 3M has recently removed the following LDL statement from all new literature.

3M PRODUCT MONOGRAPH FOR ALDARA

L D L SAFETY STATEMENT PRIOR TO 2003

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 1600mg/m^2 .***

Commentary

Below is most likely the reason 3M chose the "rabbit species" to represent the LDL safety statement in their FDA approval process. The following statement also must call into question the use and validity of all other rabbit species data found scattered throughout the 3M monograph and indeed most of the worldwide research and drug approval communities, all of which rely upon accurate data.

IMIQUIMOD APPLIED TOPICALLY: A NOVEL IMMUNE RESPONSE MODIFIER AND NEW CLASS OF DRUG

By: R.L. Miller, J.F. Gerster, M.L. Owen, Herbert Slade, M. A. Tomai
All are Senior Officials of 3M Pharmaceuticals, St. Paul, Minnesota

"Finally, in a rabbit papillomavirus infection model in rabbits, topically applied imiquimod was ineffective, ***which is likely due to the drug's inability to induce IFN and possibly other cytokines in this species****."*

Commentary

The FDA explicitly warns all pharmaceutical companies against using **"irrelevant animal species"** in their research data. Irrelevant animal species are those species in which the drug under investigation, IQ in this case, results in little to no measurable pharmacological action within the animal during direct exposures to the drug under investigation.

The monkey as well as other species did die much quicker and with far less exposures to IQ than the rabbit, which 3M states, was unaffected by IQ stimulation. None of the rabbit data should have been included in the FDA approval process, yet, it was heavily relied upon by 3M to demonstrate numerous safety and efficacy criteria for Aldara.

SCIENTIFIC DISCUSSION

By: Laboratoires 3M Sante' , France

Toxicology Statement

Single dose toxicity *of imiquimod was studied in mice, rats and monkeys. These studies indicated a high degree of safety. Adverse effects were limited to the central nervous system resulting in a number of clinical signs, usually convulsions, prior to death.*

In two dermal toxicity studies in rabbits with doses of 2000 and 5000 mg/kg under occlusion there were ***no deaths and no signs of toxicity*** *other than mild transient erythema at the application site.*

Commentary

3M consistently and knowingly uses the irrelevant data from the rabbit to demonstrate exaggerated safety profiles for Aldara. Patients and their treating physicians rely heavily upon the accuracy of this safety statement when considering the use of Aldara in their treatments and medical practices.

This safety statement only contributes to the growing misconception in today's medical community that simply because it is a topically applied drug, Aldara has no possibility of causing injury to its users regardless of how grossly it is applied or misused.

U. S. Federal Testimony – Beasley vs 3M Pharmaceuticals etal

by: 3M's Dr. James Lee – 3M Drug Surveillance and Information:

Question:
For instance, the monkey in your study died sooner than the rabbit did?

Lee's Answer:
That's correct.

Question:
Do you know why that is?

Lee's Answer:
The monkey seemed more sensitive to the effects of the Imiquimod.

Question:
Was the rabbit the least sensitive of all the animals to the Imiquimod from what your studies referenced?

Lee's Answer:
Of all the animal species?

Question:
Right.

Lee's Answer:
That's correct.

Question:
Why did 3M make the decision to reference a rabbit versus a monkey or some other more sensitive animal in its packaging?

Lee's Answer:
I don't__I don't know.

SYSTEMIC SIDE-EFFECTS INDUCED BY IQ

Commentary

3M's Dr. Rohan (see testimony) has stated that systemic side-effects experienced during IQ exposures are the combined effects of both IQ molecules and the elevated levels of IQ induced cytokines that have reached the systemic compartment via of the skin lesions where Aldara is being **topically** applied.

Thus, according to Dr. Rohan, percutaneous absorption has occurred at this point.

University experts in the fields of rheumatology and immunology have all unanimously concluded (see poll results) that if this scenario described by Dr. Rohan is allowed to persist for a period of 21-days or longer, this systemic action can overcome tolerance and lead to one or more autoimmune disorders.

An example of an IQ induced autoimmune disorder is pemphigus. (see page 13)

The author of this monograph has also surveyed many users of Aldara who have been injured in various ways by Aldara during their treatments. One common attribute shared by all injured users in the survey is the fact that until experiencing the ill effects from their treatments with Aldara they all had enjoyed very healthy medical histories with few reports of prior illnesses. This leads to the supposition that the immune systems of these individuals must therefore be highly reactive and/or efficient at identifying, targeting, and eradicating the earliest signs of foreign invaders or antigens infecting their bodies. In this case, this portion of the population would be expected to have an immune system that is highly sensitive at having its production of cytokines, (immune response), rapidly increased to meet any new challenge from infections. Thus, support for how this segment of the population remains so healthy when others remain sickly.

It is theorized by the author that when Aldara is applied to innate highly reactive immune systems, IQ mechanisms drive levels of induced cytokines far above those levels found induced in lower respondents to the drug. This would explain why these users experience both early, and violent, IQ induced inflammatory responses at the treatment site, and why these users develop more severe systemic side-effects that lead to their long-term injuries. Low to moderate responders to Aldara seem to have few or no systemic side-effects during their treatments and almost never report experiencing long-term effects from their use of Aldara.

Further indications of 3M knowing of systemic involvement during topical Aldara use, whether in HPV or skin cancer treatments, comes from the following disclosure made in the FDA Approval Data:

6.5.6 Laboratory Abnormalities:

Clinical laboratory results were compared prestudy, week 8, and at the end of treatment. Statistically significant changes from prestudy to the end of treatment were identified for hematocrit, WBC, SGPT, sodium chloride, albumin, and cholesterol in the imiquimod 5% group. Two patients in the imiquimod 5% group experienced a drop in WBC's count below 3,000 during the study treatment.

The study above was conducted on a reduced regimen of 3X / week or every other day and on HPV genital warts which is the least likely regimen and use of Aldara for creating systemic side-effects in the host user. Yet, as noted, serious and significant laboratory changes were induced by this regimen and use of Aldara during this study treatment. Through extrapolation, as further supported by Study 1005-IMIQ, use of Aldara in treatments such as sBCC skin cancers or for any other condition by which 3M requires the use of Aldara more frequently than 3X / week can only exacerbate these recorded abnormal changes in clinical laboratory results, for the more frequent user groups.

It is also worth noting that these, and other changes in clinical laboratory tests results can only be the result of imiquimod's systemic wide physiological influences from both direct and indirect drug action and/or **drug induced activity in circulation.** Thus 3M's argument, dating as far back as the original 1997 HPV FDA approval, where they state "percutaneous absorption is unlikely due to minimum percutaneous drug absorption during treatments" is now, and was known to be then, an inaccurate and invalid statement.

In fact it is virtually impossible, in the context of a discussion on Aldara, for the user to experience systemic side-effects during their topical treatments and have those side-effects caused by anything other than **a significant percutaneous absorption of imiquimod molecules that have reached blood circulation.**

VARIOUS REMAINING ISSUES

Absorption

3M's Dr. Rohan testimony:

Question:
If somebody had an open wound on their face or head and they were applying the cream (Aldara) to an open wound, would that increase the chance of the chemicals getting into the person's bloodstream?

Rohan's answer:
Yes, I think it could.

3M's Dr. Lee testimony:

Question:
3M doesn't have any particular data that would analyze the absorption rate of applying Aldara on an open wound as opposed to intact skin?

Lee's answer:
No

Commentary

Both the data and 3M testimony describes an IQ treatment site consisting of erosions and ulcerations of the skin which are the results of drug induced actions that extends well below the "basal layer" of the skin. This lower breach of the epidermis exposes the layers consisting of blood enriched capillaries, etc., which too will eventually become part of the erosive process of drug induced actions ,and upon these capillary walls being breached will turn the treatment site into the bloody, weeping and draining site so commonly seen by physicians and their patients sometime during their treatments. Once the site reaches this stage of ulceration, Aldara and any cytokines induced at/in the site are then being delivered "subcutaneously" and therefore is being made available for direct delivery into blood circulation. Something, 3M publicly declares does not happen. Instead, this is a "most common" occurrence rather than a rarity as 3M data might suggest.

In their testimony, 3M describes this very process of erosion occurring in their HPV trials as well as their AK/BCC skin cancer trials. High responders to IQ virtually all experience severe ulcerations soon after initial applications of Aldara. 3M testimony also discloses that so-long as you apply Aldara to an ulcerated open lesion this erosive drug action will continue, with each application driving the cellular destruction even deeper. This process eventually assures subcutaneous delivery of IQ molecules and induced cytokines into the systemic compartment creating an environment conducive for the occurrence of very serious side-effects.

Further, the above process of erosion is quickly initiated on the face of high responders due to facial skin thicknesses of only .5mm or less. Also, a contributing factor that catalyzes this process of erosion is the fact that, contrary to 3M's public position on the subject, in early 3M human clinical trials, Aldara was found to mount a very violent attack upon sun-damaged skin found to be free of skin cancer lesions. It seems that IQ unleashes its "non-specific" process on sun-damaged skin which can be found literally everywhere on the face, neck, hands, and other routinely unprotected parts of the body from UV sun rays.

IMIQUIMOD CREAM SHOWS PROMISE IN BASAL CELL CANCER
3M Sponsored Research
by: Dr. Karl Beutner 1999

*"The biggest surprise was the **ability of imiquimod to induce inflammation in sun-damaged skin.**" This effect was unexpected in large part because past experience with imiquimod has been in treatment of anogenital warts in unexposed anatomic sites.*

3M HUMAN STUDY 1270

The sun-damaged skin had a lower incidence and severity of irritation compared to the normal skin.

Commentary

Historically, each time the independent research community discovers negative attributes for Aldara/imiquimod 3M, soon after, develops specific clinical trials aimed at refuting all prior negative claims for the respective negativity called into question. Dr. Beutner in 1999 found, ***to his surprise***, IQ induces inflammation in sun-damaged skin, which prompted 3M to design Study 1270 which found that Dr. Beutner must have evidently been mistaken in his study. The question is why should the drug manufacturer data, which cannot be impartial, automatically be assumed more valid over independent research studies. Another confusing but interesting point is that both of the above conflicting statements are both derived from 3M sponsored studies. Is this an internal correction by 3M of yet another earlier discovered negative attribute for Aldara that needed to be corrected?

Misuse and abuse of words in data:

Dr. Lee Testimony:
Question:
Can you define intercurrent?

Lee's answer:
Intercurrent means __ we define it as something that is going on at the same time or with some overlap.

Commentary

Intercurrent:
During clinical trials, subjects present trial investigators with many serious medical symptoms that, if classified as being related to the drug under investigation, must be documented and reported to the FDA Adverse Event

Reporting System (AERS). However, the investigators also have, at their sole discretion, the ability to prevent any number of these events from being reflected in the final publicized clinical reporting data by simply labeling the event of their choice with the word "intercurrent". This labels these symptoms and conditions, as investigators so choose, as events "going on at the same time or with some overlap", but, are not in any way related to the clinical trial nor the drug's action under investigation, even when they are.

Upon having these most serious events labeled "intercurrent" only those events taking place during the trial that are found to be directly attributable to the drug action (which are usually found to be much less serious) need be reported in the final publicized release of the clinical trial results. The "intercurrent" serious events are usually not mentioned at all and certainly are not reflected in the FDA reporting system as having any connection with the drug under investigation.

This method of "filtering" clinical trial data that eventually reaches the FDA - AERS report form for a drug must then be questioned as being incomplete and invalid so-long as the accuracy and completeness of this FDA-AERS report for the drug is strictly controlled by the manufacturer of the drug under study; who's incentive lies in developing the most positive results in regard to a serious adverse effects safety profile for their drug.

Thus, the public can never know by reviewing the FDA-AERS report or any other listing of serious side effects for Aldara if indeed it is a complete, and accurate accounting of **ALL** reported serious side-effects for Aldara nor how many really serious events have missed being reported by being labeled "intercurrent".

Intercurrent is also utilized, by 3M, in post-approval reports of SAE's by patients.

3M's Dr. Lee testimony:

Question
In the clinical trials, pre-approval, are all of the reported symptoms listed in the data?

Lee's answer
They are. They're collected on what are called Case Report forms and they are line listed. They're put into a database and they're all collected and line listed into the NDA.

Question
And is there some effort made in that process to determine whether or not there are certain symptoms that are not related to the drug?

Lee's answer
There are comments that are put in, coded by the investigator and ***the investigator gets the last call whether it's related or not****.*

Example: FDA Approval Data:

5.5.4 Serious and severe adverse events:

Clinically significant severe adverse event possibly related to 5% imiquimod cream was headache by one patient. Chest pain, myalgia, numbness of extremities, influenza-like symptoms, and fever were also reported, however, ***these events were judged not to be related to the study treatment.***

Commentary:
All above reported but excluded side-effects in 5.5.4 were at the time known listed side-effects with Aldara yet ruled "intercurrent" by researchers in this data.

Non-Specific drug action:

Commentary
Testimony by 3M's Dr. Slade and Dr. Rohan has clearly described their drug IQ as one that has no ability to select a specific target from which to mount a specific immune response toward.

They also describe IQ as being unpredictable and in some instances unreliable across the patient user population. Some have little or no response while others end up seeking emergency medical treatment and/or hospital care.

3M's Dr. Lee Testimony

Question
Does that mean that the cytokines and the activation of the immune system are going to go in and it may affect different things, it's not just going to target in on one specific thing?

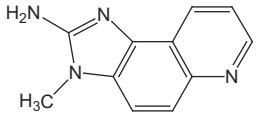
Lee's answer
It__what__what it really does is it ___it doesn't___at least, we don't think, it does not induce reaction toward the body's own normal cells.

Either 3M has full knowledge that IQ is capable of stimulating normal immune systems to the point of breaking tolerance, thus inducing autoimmunity, and they simply can not afford to admit it, or, according to Dr. Lee's statement above, they actually don't know if it can or not. Either way, this is much too important an issue for patient safety to rely upon "fate" and a manufacturer's professional opinion grounded in such little understanding of its drug's mechanism of operation or their unwillingness to disclose their full knowledge about the drug.

We have learned in this monograph that IQ is capable of breaking tolerance and leaving its users with pemphigus, a dreaded autoimmune condition.

END

2-AMINO-3-METHYLIMIDAZO[4,5-f]QUINOLINE (IQ)
CAS No. 76180-96-6
First listed in the *Tenth Report on Carcinogens*



CARCINOGENICITY

2-Amino-3-methylimidazo[4,5-*f*]quinoline (IQ) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of benign and malignant tumor formation at multiple tissue sites in multiple species of experimental animals (IARC 1993). Oral exposure of rats to IQ induces neoplasms of the mammary gland, liver, small intestine, clitoral gland, oral cavity, and Zymbal gland in females and neoplasms of the liver, skin, colon, small intestine, oral cavity, and Zymbal gland in males. Oral exposure of mice to IQ induces neoplasms of the lung, liver, and forestomach in males and females. Intraperitoneal injection of IQ in mice and oral exposure in cynomologus monkeys causes liver tumors.

No adequate epidemiology studies have been reported that would indicate a human cancer risk specifically associated with exposure to IQ or other heterocyclic amines (HCAs). However, published epidemiology studies provide some indication that human cancer risk is related to consumption of broiled or fried foods that may contain IQ and/or other HCAs.

OTHER INFORMATION RELATING TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Studies have uniformly shown that IQ is genotoxic in a wide variety of bacterial, plant, and mammalian test systems, mainly with metabolic activation, and in animals *in vivo* (IARC 1993). IQ induces DNA and chromosomal damage in various cultured human cells, including mutations, chromosomal aberrations, sister chromatid exchange, micronuclei, and unscheduled DNA synthesis. IQ is metabolized to reactive intermediates via acetylation and hydroxylation. *N*-acetoxy-IQ degrades to an unstable nitrenium ion that can bind to DNA. In animals given IQ, DNA adducts have been found in many tissues, including those where IQ-induced tumors occur. All animal species studied have been found to metabolize IQ to products that react with DNA, as do human mammary gland cells and liver microsomes *in vitro.*

No available data suggest that mechanisms thought to account for IQ's induction of tumors in experimental animals would not also operate in humans.

PROPERTIES

IQ is a light tan crystalline solid. It is stable under moderately acidic and alkaline conditions and in cold, dilute aqueous solutions when protected from light (IARC 1986). It is rapidly degraded by dilute hypochlorite (IARC 1993). It is insoluble in water (at 20°C) and soluble in dimethylsulfoxide, 95% ethanol (at 16°C), methanol, acids, and alcohol.

USE

IQ is one of a number of HCAs found in cooked food, primarily in meats and fish. It has no commercial uses, but it is used for research purposes.

PRODUCTION

IQ is produced commercially in small quantities for research. Chemical synthesis was first reported in 1980. 5,6-Diaminoquinoline was reacted with cyanogen bromide, which produced a cyclic intermediate that was converted to the tetramethyl ammonium salt and then heated under reduced pressure to form IQ. The IQ was purified by sublimation, silica-gel column chromatography, and crystallization from aqueous methanol (IARC 1993).

EXPOSURE

The most likely route of human exposure is through consumption of food containing IQ, such as broiled or fried beef, fish, or eggs (IARC 1993). IQ also is present in cigarette smoke (Yamashita *et al*. 1986). Estimated daily exposure of the U.S. population to IQ and other HCAs ranges from 100 ng to 10 μg, based on analysis of various foodstuffs. Overall U.S. exposure to IQ is difficult to estimate because it depends on the type of meat, cooking temperature, and manner of preparation (Turesky *et al*. 1993).

Occupational exposure to IQ may occur where employees prepare or serve broiled or fried foods, such as beef, fish, or eggs, but no studies that examined this question were found in the literature. It is not known whether exposure to IQ by ingestion, inhalation, or dermal contact would occur in this setting.

REGULATIONS

OSHA regulates 2-amino-3-methylimidazo[4,5-*f*]quinone under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 12.

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DIARY OF EVENTS DURING MY USE OF ALDARA

• **On January 26, 2000,** at the age of 51, I received a perfect score on my yearly complete physical and was enjoying very good health, working 14 – 16 hour days in my construction business of 26+ years. I had gone years without even so much as a common cold.

• **On January 28, 2000**, I began treating the BCC on my forehead with Aldara.

• The treatment site was raw and inflamed on the 4th day

• **6th day**, the site was an open, weeping, bloody wound the size of a credit card and I was experiencing serious flu-like symptoms.

• **7th day**, I was rushed to the emergency room with a severe nose-bleed, spitting up blood, severe head congestion, nauseated, joint and muscle pains, neck pains, coughing, shortness of breath, stomach cramps, pounding headache and lower back pain.

• **9th day**, Dermatologist stopped the application of Aldara in open wound and prescribed additional applications to five other BCC's on my face. He was not at all suspicious of the many serious symptoms I was presenting.

• **11th day**, I had all the same symptoms described above plus diarrhea, fainting spells, blurred vision, metallic taste in my mouth, hoarseness, lower back-pain, and trouble with my balance when walking (all are known side-effects of Aldara). I had constant whole body pains and remained in bed most of the day and had lost 13-pounds.

• **21st day**, I took myself off Aldara due to the severe complications. By this time I was bedridden, still loosing weight, nauseated, weak, and highly disorientated along with all the other symptoms described above. The whole body pain was unbearable.

• **31st day**, I had lost a total of 20-pounds and my symptoms were still in full force. Between Ensure and regular food, I was eating 3,000 to 4,000 calories / day. By this time, my physicians in oncology, pulmonary, gastroenterology, and more were frantically running all kinds of tests and scans trying to reach an understanding of what was causing all my serious symptoms. I was placed on guarded watch for 30-days and began responding to treatments. Eventually, over months, I regained my weight and was able to function once again on my own.

• **The following year**, I had numerous lengthy stays in the hospital for treatments consisting of mysterious internal infections and inflammations, abnormalities in blood tests, and dehydration. Over time, tests would finally reveal systemic autoimmune like disorders, fibromyalgia, unnatural degenerative hearing losses in both ears, suspected cytokine involvement in systemic muscle and joint disorders causing severe whole body pain from inflammation, severe dry eyes, a neurological condition causing severe headaches, celiac disease, and out breaks of blisters in mouth and on my scalp.

• **Today**, nine years later, I am still unable to work, still have severe whole body pain from joint and muscle inflammation, stiffness, headaches, fatigue, diarrhea, lower back pains, trouble walking distances, lost even more of my hearing, memory loss, complications from both fibromyalgia and celiac disease, irritable bowel syndrome, Parkinson's Disease, sjogrens syndrome, stomach cramps, explosion of BCC's and AK's and never have a good day regardless of how hard I try.

None of my existing conditions are found in either side of my family's medical histories.

I doubt this is all a coincidental list of diseases and conditions I would have been expected to contract in the absence of my use of Aldara/imiquimod on a simple facial sBCC back in Feburary of 2000.