TRICHLOROACETIC ACID

Pharmacy Compounding Advisory Committee
November 3, 2016

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PCCA Director of Pharmacy Consulting
Current Use of TCA

[ L I T E R A T U R E R E V I E W ]

Genital Warts
A Comprehensive Review

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Abstract
External genital warts, also known as condylomata acuminata, are extremely common, with between 500,000 to one million new cases diagnosed each year in the United States alone. To date, more than 120 distinct subtypes of human papillomavirus have been identified. Human papillomavirus types 6 and 11 rarely give rise to cervical cancers, but are responsible for 90 percent of the cases of genital warts. The current treatment options are largely centered upon removal of the warts rather than elimination of the underlying viral infection. A wide range of therapies are presently in use, which are highly variable and can differ dramatically with respect to cost, side-effect profiles, dosing schedules, duration of treatment, and overall effectiveness. As of yet, no definitive therapy has emerged as the ideal standard of care in the treatment of genital warts, and therapy selection generally occurs in a patient-specific manner.
<table>
<thead>
<tr>
<th>TREATMENT TYPE</th>
<th>MECHANISM OF ACTION</th>
<th>ADMINISTERED BY</th>
<th>PREGNANCY SAFETY</th>
<th>LEVEL OF EVIDENCE</th>
<th>CLEARANCE</th>
<th>RECURRENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOPICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Podophylloin</td>
<td>Anti-wart lignans</td>
<td>Patient</td>
<td>Unknown</td>
<td>A</td>
<td>45–7734,36</td>
<td>38–6538</td>
<td>Cost-effective home treatment</td>
</tr>
<tr>
<td>Imiquimod 5% cream</td>
<td>Induces secretion of cytokines that reduce HPV DNA viral load</td>
<td>Patient</td>
<td>Unknown</td>
<td>A</td>
<td>5645</td>
<td>1345</td>
<td>Lengthy duration and sporadic dosing frequency can affect compliance</td>
</tr>
<tr>
<td>Imiquimod 3.75% cream</td>
<td>Induces secretion of cytokines that reduce HPV DNA viral load</td>
<td>Patient</td>
<td>Unknown</td>
<td>A</td>
<td>28–3341</td>
<td>1541</td>
<td>New formulation with more intuitive dosing regimen</td>
</tr>
<tr>
<td>Sinecatechins 15% ointment</td>
<td>Possess antitumor, antiviral, antioxidant effects</td>
<td>Patient</td>
<td>Unknown</td>
<td>A</td>
<td>5835</td>
<td>6–935</td>
<td>Can often take 16 weeks to elicit positive response</td>
</tr>
<tr>
<td>Podophyllin</td>
<td>Anti-wart lignans</td>
<td>Patient</td>
<td>No</td>
<td>C</td>
<td>42–5067</td>
<td>46–6088</td>
<td>Not generally recommended for EGW treatment</td>
</tr>
<tr>
<td>5-FU</td>
<td>Inhibits key enzyme in DNA replication</td>
<td>Physician</td>
<td>No</td>
<td>C</td>
<td>10–5044</td>
<td>5041</td>
<td>Sometimes used for urethral warts</td>
</tr>
<tr>
<td><strong>DESTRUCTIVE AND SURGICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>Chemically destructive acids</td>
<td>Physician</td>
<td>Yes</td>
<td>B</td>
<td>7049</td>
<td>1840,41</td>
<td>High clearance rates with relatively low morbidity</td>
</tr>
</tbody>
</table>
Trichloroacetic acid (TCA) 80–90% solution (Grade B).

TCA is a chemically destructive acid that burns, cauterizes, and erodes the skin and mucosa. Generally prepared in 80 to 90% solutions, TCA necessitates administration by the physician. Successful treatment of warts can occasionally occur with as little as a single dose; however, more frequently, several applications are required.

TCA is an inexpensive, cost-effective treatment that does require prolonged usage and regimen adherence. The destructive nature of the product frequently extends beyond the superficial wart to encompass the underlying viral infection providing for clearance rates that have been estimated at 70 to 80 percent with high recurrence rates of 36 percent. An obstetric study that evaluated the use of 85% TCA in 50 female subjects with external genital warts showed that all subjects were cleared of all lesions after a treatment period that ranged from 2 to 5 months. None of the patients had recurrence or new lesions during the first six-month follow-up period. In the second six-month follow-up period, nine patients (18%) were diagnosed with recurrent lesions. Although transient burning pain during therapy was commonly experienced, none of the patient population discontinued therapy.

Additionally, the low danger of systemic absorption allows for safe application during pregnancy. The main side effects of acid treatments involve pain or burning during administration as well as destruction of the healthy tissue surrounding the wart. The latter can be minimized by washings with soap and sodium bicarbonate immediately following over-application, and dermal injury or scarring is rare. Occasionally, tissue destruction can result in pain, ulceration, and crust formation. High success rates and relatively low morbidity make acetic acid therapy a recommended treatment option for CA.

Current Use of TCA

- IUSTI 2011 GW Guidelines
  - European Guideline for the Management of Anogenital Warts
  - This guideline has been produced on behalf of the following organisations: the European Branch of the International Union against Sexually Transmitted Infections (IUSTI Europe); the European Dermatology Federation (EDF); the Union of European Medical Specialists (UEMS).
  - Accessed October 20, 2016

**Home therapy**
- Podophyllotoxin (0.15% cream or 0.5% solution)
- Imiquimod (5% cream).

**Clinic therapy**
- Cryotherapy
- Trichloroacetic acid
- Electrosurgery / scissors excision / curettage / laser
Current Use of TCA

- CDC Recommended Regimen for External Anogenital Warts
  - Accessed October 20, 2016

Provider-Administered:

- Cryotherapy with liquid nitrogen or cryoprobe
  - OR
- Surgical removal either by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery
  - OR
- **Trichloroacetic acid (TCA) or bichloroacetic acid (BCA)** 80%-90% solution

Trichloroacetic acid (TCA) and bichloroacetic acid (BCA) are provider-applied caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly. TCA solution has a low viscosity comparable with that of water and can spread rapidly and damage adjacent tissues if applied excessively. A small amount should be applied only to the warts and allowed to dry (i.e., develop white frost on tissue) before the patient sits or stands. If pain is intense or an excess amount of acid is applied, the area can be covered with sodium bicarbonate (i.e., baking soda), washed with liquid soap preparations, or be powdered with talc to neutralize the acid or remove unreacted acid. TCA/BCA treatment can be repeated weekly if necessary.
TRICHLOROACETIC ACID

Acidum trichloroaceticum

CgHsO.
N, 15.3

DEFINITION
5.2.2.3-Trichloroacetic acid.

CHARACTERS
Appearance: White or almost white, crystalline mass or colourless crystal, very hygroscopic. Solubility: Very soluble in water, in ethanol (96 per cent) and in acetic anhydride.

IDENTIFICATION
First identification:
A: Infrared absorption spectrophotometry (2.2.22).

B. To 5 ml of solution S (see Tests) add 2 ml of water and 5 ml of strong sodium hydroxide solution. Shake vigorously and heat, in a water bath at 60-65°C, for 5 min.

C. Solution S is strongly acidic (2.2.14).

78739

Solution S. Disperse 2.5 g in water R and dilute to 25 ml with the same solvent.

Appreciation of solution. Solution S is clear (2.2.23) and not more intensely colored than reference solution WT (2.2.2, Method II).

Chlorides (2.4.1). Maximum: 0.2 per cent.

Dilute 5 ml of solution S to 50 ml with water R.

Analyzed solution (2.4.1). Maximum 0.1 per cent, determined on 1.0 g.

ASSAY
Dissolve 0.100 g in 30 ml of water R. Titrate with 0.1 M sodium hydroxide solution, determining the end point potentiometrically (2.2.23).

1 ml of 0.1 M sodium hydroxide solution is equivalent to 0.745 mg of CgHsO.

STORAGE
In an airtight container.

01/20001479

TRIETHYL CITRATE

Triethyl citras

C1130.

DEFINITION
Triethyl 2-hydroxypropanoate 1,3,5-trikisole.

CHARACTERS
Appearance: Colourless, viscous, olfactory or almost odorless, hygroscopic liquid.

Solubility: Very soluble in water, in ethanol (96 per cent) and slightly soluble in fatty oils.

IDENTIFICATION
First identification:
A. Infrared absorption spectrophotometry (2.2.22).

B. To 2 g of the substance in ethanol (96 per cent) R add 3 ml of glacial acetic acid R and 4 ml of anhydrous acetic anhydride and 0.5 ml of ethyl alcohol. Heat the mixture gently at 60°C, 1 min.

D. To 0.5 ml of the mixture gives the reaction of ester (2.2.1).

PH 2.3

Appreciation. The substance in a volume of 5 ml is not more intensely colored than reference solution WT (2.2.23).

Acidity. Disperse 2 g with 0.1 ml of glacial acetic acid to 50 ml of water and 0.5 ml of anhydrous acetic acid. Dilute the mixture with 20 ml of water R and 0.05 ml of the solution of 2 molar sodium hydroxide. Add 0.5 ml of glacial acetic acid R. To the mixture add 5 drops of phenolphthalein solution R and titrate with 0.1 M sodium hydroxide. Titrate with 0.1 M sodium hydroxide solution an equal number of ml of the solution of 2 molar sodium hydroxide. The result is expressed in milliliters of 0.1 M sodium hydroxide solution. The result is expressed in milliliters of 0.1 M sodium hydroxide solution. The result is expressed in milliliters of 0.1 M sodium hydroxide solution. The result is expressed in milliliters of 0.1 M sodium hydroxide solution.

Related substances. Use the chromatography (2.2.23) and the identification procedure.

See also the monograph (Appendix 2) on the preparation of the substance.
Trichloroacetic Acid

\[
\text{C}_2\text{H}_3\text{Cl}_2\text{O}_2 \quad 163.39
\]

Acetic acid, trichloro-.
Trichloroacetic acid \[76-03-9\].

Trichloroacetic Acid contains not less than 99.0 percent and not more than 100.5 percent of \(\text{C}_2\text{H}_3\text{Cl}_2\text{O}_2\), calculated on the dried basis.

Caution—Trichloroacetic Acid is highly corrosive to the skin and mucous membranes.

Packaging and storage—Preserve in tight containers, at controlled room temperature.

Identification—When heated with a solution of an alkali hydroxide, it is decomposed, with the formation of an alkali carbonate and chloroform. The addition of a few drops of a saturated solution of aniline to the heated mixture produces the disagreeable odor of phenyl isocyanide [Caution—poisonous].

Loss on drying (731)—Dry it over silica gel for 18 hours: it loses not more than 1.0% of its weight.

Residue on ignition (281): not more than 0.05%.

Chloride (221)—A 1.0-g portion shows no more chloride than corresponds to 0.50 mL of 0.020 \(N\) hydrochloric acid (0.035%).

Sulfate (221)—A 0.50-g portion shows no more sulfate than corresponds to 0.40 mL of 0.020 \(N\) sulfuric acid (0.080%).

Assay—Place about 4 g of Trichloroacetic Acid in a tared, glass-stoppered conical flask, and weigh accurately. Dissolve in about 40 mL of water, add phenolphthalein TS, and titrate with \(1 \, N\) sodium hydroxide VS. Each mL of \(1 \, N\) sodium hydroxide is equivalent to 163.4 mg of \(\text{C}_2\text{H}_3\text{Cl}_2\text{O}_2\).
THANK YOU

Questions from the Committee?
Fagron North America, IACP, NCPA: Nominators

Pharmacy Compounding Advisory Committee review: Kojic Acid
Kojic Acid

- A fungal metabolite of certain species of Acetobacter Aspergillus, and Penicillium

- Depigmenting properties originate from a potent inhibition of tyrosine by chelating copper at the active site of the enzyme\(^1\)

- Skin lightening effects are not irreversible, it’s a slow competitive inhibition of tyrosine\(^1\)

- Acts as an antioxidant and free radical scavenger\(^2\)

- Has antibacterial activity\(^2\)


Safety

- In vivo mammalian dominant lethal assay, kojic acid was proven **negative**\(^1\)

- In a **14 year dermatological study** in humans, kojic acid was shown to have:
  - No adverse local effects
  - No adverse systemic effects\(^2\)

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Safety

- Six postmenopausal volunteers received a single dose of Kojic acid topical cream
- The application of 1% cream (500 mg dose) was applied to the hands and face
- Kojic acid did not undergo enterohepatic circulation and resulted in a maximum plasma level of 1.54 ng/ml
- No adverse event were observed in the participants

Davies D.J. Kojic Acid - In vitro Percutaneous Absorption of [14C]-Kojic Acid in a Leave-on Skin Care Formulation through Human Dermatomed Skin. Study Number QD0849/003. Report JV2136-REG, issued 24/01/2011
Safety

• Kinosita et al provides data that exposure in Japanese populations to Kojic acid through consumption of Miso and soy sauce alone can be as much as 103 mg/day

• Kojic acid is regarded by the Japanese Ministry of Health and Welfare as safe to be added to foods
## Amounts of Kojic Acid in foods

### TABLE 1

**Reports of Kojic Acid Occurrence**

<table>
<thead>
<tr>
<th>Natural source</th>
<th>Concentration</th>
<th>Source organism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maize (Zurich area)</td>
<td></td>
<td></td>
<td>Steiner et al., 1991</td>
</tr>
<tr>
<td>Maize (South Africa)</td>
<td></td>
<td></td>
<td>Dutton and Westlake, 1985</td>
</tr>
<tr>
<td>Wheat bran, crushed soybeans</td>
<td></td>
<td></td>
<td>Kharchenko et al., 1986</td>
</tr>
<tr>
<td>Rice</td>
<td></td>
<td>Aspergillus flavus</td>
<td>L'vova et al., 1984</td>
</tr>
<tr>
<td>Animal feed</td>
<td>37.6–40.5 ppm</td>
<td>A. flavus</td>
<td>Kharchenko and Yatsyshin, 1984</td>
</tr>
<tr>
<td>Animal feed</td>
<td></td>
<td>A. oryzae</td>
<td>Kharchenko and Yatsyshin, 1984</td>
</tr>
<tr>
<td>Animal feed</td>
<td></td>
<td>A. nidulans</td>
<td>Kharchenko and Yatsyshin, 1984</td>
</tr>
<tr>
<td>Animal feed</td>
<td></td>
<td>A. fumigatus</td>
<td>Kharchenko and Yatsyshin, 1984</td>
</tr>
<tr>
<td>Corn</td>
<td></td>
<td></td>
<td>L'vova et al., 1981</td>
</tr>
<tr>
<td>Japanese fermented foods</td>
<td>40 mg/ml (in medium)</td>
<td>A. oryzae</td>
<td>Manabe et al., 1981</td>
</tr>
<tr>
<td>Corn</td>
<td></td>
<td>A. tamarind, A. flavus</td>
<td>Manabe et al., 1981</td>
</tr>
<tr>
<td>Danish blue cheese</td>
<td></td>
<td>A. flavus</td>
<td>Scott, 1978; Lee et al., 1986</td>
</tr>
<tr>
<td>Butternut squash</td>
<td></td>
<td>A. fumigatus Fres.</td>
<td>Moubasher et al., 1979</td>
</tr>
<tr>
<td>(unprocessed not refrigerated)</td>
<td></td>
<td>Penicillium</td>
<td>Torrey and Marth, 1977</td>
</tr>
<tr>
<td>Spice</td>
<td></td>
<td>Aspergillus</td>
<td>Torrey and Marth, 1977</td>
</tr>
<tr>
<td>Human skin</td>
<td></td>
<td>Aspergillus spp. (14 isolates) and Penicillium 6 isolates) spp.</td>
<td>Kandem and Percefois, 1980</td>
</tr>
<tr>
<td>Buffalo pneumonia</td>
<td></td>
<td></td>
<td>El-Kady et al., 1984</td>
</tr>
<tr>
<td>Yeast extract—sucrose medium</td>
<td>57–59 mg/ml</td>
<td>A. fumigatus</td>
<td>Wei et al., 1991</td>
</tr>
<tr>
<td>Yeast extract—sucrose medium</td>
<td>0.133–3.4 mg/ml</td>
<td>A. candidus ATCC44054</td>
<td>Gupta et al., 1971</td>
</tr>
<tr>
<td>Cocoa sweat or juice</td>
<td>22 mg/ml</td>
<td>A. flavus ATCC9179</td>
<td>El-Sharkawy, 1995</td>
</tr>
<tr>
<td>Sago starch</td>
<td>23.5 mg/ml</td>
<td>Calcium alginate immobilization</td>
<td>Rosfarizan et al., 1998b</td>
</tr>
</tbody>
</table>

Safety

- Penetration studies on human skin found the flux rate for kojic acid at 24 hours to be 0.142-0.265 ug/cm² or 0.698% of the applied dose¹

- No histopathological changes were associated with it. Based on the changes observed in lymphocytes and white blood cell counts a NOEL value of 100 mg/kg/day was established²

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1. Fukase H. Percutaneous absorption study of Kojic Acid in humans. CPC Clinic, Medical facility, Kagoshima, Japan, April 28, 2005 (unpublished).

Safety

- **107** patients with chloasma (tan or dark discolorations) applied a 2.5% kojic acid cream twice daily for a mean period of **2 months**
  - Only **2** developed skin sensitivity
  - Patch testing revealed that the hyper sensitivity seen in the **2** patients was due to the vehicle

Evidence of Safety

- **NOAEL** or no observed adverse effect level is determined at which there is no biological or statistically significant increase in frequency or severity of an adverse effect.

- In clinical trials it can be used to establish a safe starting dose.
## Face

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum absorption through the skin</td>
<td>A (µg/cm²) = 8.39 µg/cm²</td>
</tr>
<tr>
<td>Skin Area surface</td>
<td>SAS (cm²) = 565 cm²</td>
</tr>
<tr>
<td>Dermal absorption per treatment</td>
<td>SAS x A x 0.001 = 4.11 mg</td>
</tr>
<tr>
<td>Typical body weight of human</td>
<td>= 60 kg</td>
</tr>
<tr>
<td>Systemic exposure dose (SED)</td>
<td>SAS x A x 0.001/60 = 0.079 mg/kg</td>
</tr>
<tr>
<td>No observed adverse effect level (28 days, rat, oral)</td>
<td>NOAEL = 6 mg/kg bw/d</td>
</tr>
<tr>
<td>No observed adverse effect level extrapolated to subchronic study (6-month, rat, oral)</td>
<td>NOAEL/3 = 2 mg/kg bw/d</td>
</tr>
</tbody>
</table>

### Margin of Safety

**NOAEL / SED = 25.3**

## Hands

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum absorption through the skin</td>
<td>A (µg/cm²) = 8.39 µg/cm²</td>
</tr>
<tr>
<td>Skin Area surface</td>
<td>SAS (cm²) = 860 cm²</td>
</tr>
<tr>
<td>Dermal absorption per treatment</td>
<td>SAS x A x 0.001 = 6.28 mg</td>
</tr>
<tr>
<td>Typical body weight of human</td>
<td>= 60 kg</td>
</tr>
<tr>
<td>Systemic exposure dose (SED)</td>
<td>SAS x A x 0.001/60 = 0.120 mg/kg</td>
</tr>
<tr>
<td>No observed adverse effect level (28 days, rat, oral)</td>
<td>NOAEL = 6 mg/kg bw/d</td>
</tr>
<tr>
<td>No observed adverse effect level extrapolated to subchronic study</td>
<td>NOAEL/3 = 2 mg/kg bw/d</td>
</tr>
</tbody>
</table>

### Margin of Safety

**NOAEL / SED = 16.7**

## Face and hands

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum absorption through the skin</td>
<td>$A \ (\mu g/cm^2)$</td>
<td>8.39 $\mu g/cm^2$</td>
</tr>
<tr>
<td>Skin Area surface</td>
<td>$SAS \ (cm^2)$</td>
<td>1425 cm²</td>
</tr>
<tr>
<td>Dermal absorption per treatment</td>
<td>$SAS \times A \times 0.001$</td>
<td>10.37 mg</td>
</tr>
<tr>
<td>Typical body weight of human</td>
<td>$SAS \times A \times 0.001/60$</td>
<td>0.199 mg/kg</td>
</tr>
<tr>
<td>Systemic exposure dose (SED)</td>
<td>NOAEL</td>
<td>6 mg/kg bw/d</td>
</tr>
<tr>
<td>No observed adverse effect level (28 days, rat, oral)</td>
<td>NOAEL/3</td>
<td>2 mg/kg bw/d</td>
</tr>
</tbody>
</table>

### Margin of Safety

<table>
<thead>
<tr>
<th><strong>NOAEL / SED</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>10.1</strong></td>
</tr>
</tbody>
</table>

In the MoS calculation:

(i) A conservative value for the dermal absorption is applied (mean plus 2 SD),
(ii) A conservative NOAEL, derived from the disturbance of the HPT-axis in rats, is used,
(iii) An extrapolation factor from subacute to subchronic exposure is used.
Lack of Mutagenicity

- Kojic acid appeared to be mutagenic in bacterial gene mutant assays, but these findings could not be confirmed in the gene mutation test in hamsters or mouse lymphoma testing assay.

- Testing in sunlight had no relevant influence on mutagenic potential.

- In vivo testing showed no DNA adducts in Liver and thyroid there was no clastogenic findings in the liver stomach or colon, this suggests that Kojic acid is not DNA binding.

- Female mice dermally exposed to 0.3 – 3.0% Kojic Acid for 19 weeks, showed no initiation and promotion of potential for skin carcinogenesis.

- Kojic acid was not found to be mutagenic in in vivo gene mutation assay tests in transgenic mice.

Stability of Kojic Acid in Topical Preparations

- Studies completed in microemulsions of surfactants and lecithin showed an increase in stability at a pH of 5\(^1\)

- Kojic Acid is subject to oxidation in the presence of air and heat. Stability can be achieved with chemical antioxidants such as Sodium Metabisulfite, EDTA, Ascorbyl Palmitate and BHT

Compatibility statement Fagron Advanced Derma
Kojic acid

103165 - Kojic acid

Fagron performs chemical, physical and microbiological stability studies on Fagron Advanced Derma, based on literature and in collaboration with independent, GLP and ISO9001 certified laboratories, audited by our Global Quality Department (GQM).

Each vehicle showed to have an appropriate preservation against a wide strain of microorganisms or is a very hostile environment for microbial growth.

All APIs (Active Pharmaceutical Ingredient) and DCIs (Dermo Cosmeceutical Ingredients) were rated for their susceptibility to hydrolytic, oxidative and thermal degradation. These data were used for a classification of APIs and DCIs, and further selection of the least stable APIs and DCIs (with the highest susceptibility to hydrolytic, oxidative and thermal degradation) and relatively stable APIs (with the lowest susceptibility) for each vehicle.

The stability of these APIs and DCIs in the vehicles were analyzed by high performance liquid chromatography (HPLC), through stability-indicating methods according to the official EP/USP monograph. The combination of these results was used to determine the chemical stability of all APIs and DCIs listed in the tables.

The microbial and chemical results were compared with the physical compatibility result of the API/DCI in the vehicle. Hence the following beyond use dates were determined:

Table: Kojic acid in Fagron Advanced Derma

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Max. concentration</th>
<th>Beyond-use date</th>
<th>Storage condition(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nourivan™ Antiox</td>
<td>4%</td>
<td>30 days</td>
<td>15 - 25 °C</td>
</tr>
<tr>
<td>Fitalite™</td>
<td>4%</td>
<td>30 days</td>
<td>15 - 25 °C</td>
</tr>
<tr>
<td>STUDY</td>
<td>Design</td>
<td>Therapy Length</td>
<td>Result</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>----------------</td>
<td>--------</td>
</tr>
<tr>
<td>Garcia A, Fulton JE. <strong>The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions.</strong> <em>Dermatologic Surg.</em> 1996;22(5):443-447.</td>
<td><strong>39 patients treated with Kojic acid on one side of the face and hydroquinone on the other side of the face</strong></td>
<td>The patients applied creams on each side of the face for three months</td>
<td><strong>Fifty-one percent</strong> of the patients responded equally to hydroquinone and kojic acid. <strong>Twenty-eight percent</strong> had a more dramatic reduction in pigment on the kojic acid side; whereas 21% had a more dramatic improvement with the hydroquinone formulation.</td>
</tr>
<tr>
<td>Cotellessa C, Peris K, Onorati MT, Fargnoli MC, Chimenti S. <strong>The use of chemical peelings in the treatment of different cutaneous hyperpigmentations.</strong> <em>Dermatologic Surg.</em> 1999;25(6):450-454.</td>
<td><strong>20 patients with diffuse Melasma were treated with a solution of 50% glycololic acid and 10% kojic acid</strong></td>
<td>Treatments applied left on for 15 minutes than removed. Treatments were preformed biweekly for 3 - 6 months</td>
<td>6 patients showed complete regression and 12 showed partial. <strong>No side effects reported during or after</strong></td>
</tr>
</tbody>
</table>
### Efficacy

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Design</th>
<th>Therapy Length</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deo KS, Dash KN, Sharma YK, Virmani NC, Oberai C. Kojic Acid vis-a-vis its Combinations with Hydroquinone and Betamethasone Valerate in Melasma: A Randomized, Single Blind, Comparative Study of Efficacy and Safety. Indian J Dermatol. 2013 Jul;58(4):281-5. doi: 10.4103/0019-5154.113940. PubMed PMID: 23918998; PubMed Central PMCID: PMC3726874.</td>
<td>A simple randomized (computer generated random numbers), single center, single blinded (patients blinded and investigator aware of the intervention), parallel group comparative study comprised of 80 healthy adults of either sex clinically diagnosed as melasma attending the dermatology outpatient department of a tertiary care teaching hospital in western Maharashtra.</td>
<td>The patients applied creams on the face nightly for 12 weeks</td>
<td>With group A, that is, kojic acid 1% cream, the mean percentage improvement in MASI score was observed to be 58.72%. With group B, that is, kojic acid 1% and hydroquinone 2%, the mean percentage improvement in MASI score was 71.87%, with excellent response in 60%, good in 30% and fair and poor in 5% each. Group C (kojic acid 1% and betamethasone valerate 0.1% cream), showed the lowest (36.46%) improvement. There are no reports in literature studying the efficacy of kojic acid in combination with a topical corticosteroid. With group D (kojic acid 1%, hydroquinone 2%, and betamethasone valerate 0.1% in a cream base), the mean percentage improvement in MASI score was 54.03%, with 25% showing excellent improvement, good response in 35%, fair 35%, and poor in 5%</td>
</tr>
</tbody>
</table>
FDA approved medications

Hydroquinone

- Known instability due to oxidation
- Well known cause of ochronosis
- Possible toxic to melanocytes
- Caused cancer in rodent studies oral dosing

Topical toxicity form hydroquinone arises because it is a strong oxidant that rapidly converts to the melanocyte toxic products, p-benzoquinone. Hydroxybenzoquinone can cause permanent destruction of melanocytes

FDA approved medications

Mequinol

- competitive inhibitor of melanocytes substrates
- Not considered extremely effective
- pigmentation returns over time

Retinoids

- Strong irritant
- Dermatitis
- Erythema, dryness, and scaling
References

- Fukase H. Percutaneous absorption study of Kojic Acid in humans. CPC Clinic, Medical facility, Kagoshima, Japan, April 28, 2005 (unpublished).


- Davies D.J. Kojic Acid - In vitro Percutaneous Absorption of [14C]-Kojic Acid in a Leave-on Skin Care Formulation through Human Dermatomed Skin. Study Number QD0849/003. Report JV2136-REG, issued 24/01/2011.


- RIVM report 601516009/2002 Part II, Editors R.Luttik and S.M.G .J.Pelgrom; subpart 2: Follicular Thyroid Tumours in Rodents (M.T.M. van Raaij) with Appendix


DIINDOLYL METHANE

Pharmacy Compounding Advisory Committee
November 3, 2016

A.J. Day, PharmD, RPh
IACP member
Conclusions: DIM is a small organic molecule that is likely to be stable as a solid under ordinary storage conditions when kept away from light. The nominated substance is easily characterized with various analytical techniques, and the preparation of this compound has been well developed. The available information does not indicate concerns about the physical and chemical characterization of DIM or its use as a bulk drug substance for compounding under section 503A of the FD&C Act.

Conclusions: DIM and I3C have been studied clinically in a small number of patients. In general, gastrointestinal distress was dose limiting and no serious adverse events were reported. However, it is unclear whether data on toxicity were systematically captured in these studies, and a limited number of patients have been exposed in the clinical study setting. CAERS data suggest potential safety signals that were not identified in clinical studies. Overall, the safety profile of DIM has not been well characterized and there are potential signals for serious safety concerns.
Current Use of DIM in Compounding

• Utilized to modulate estrogen metabolism
  • Shift metabolite from 16-hydroxy towards 2-hydroxy via hydroxylation enzymes

• Not used to treat cancer

• 200mg QD is most commonly prescribed
## Certificate of Analysis

**Product:** DIINDOLYL METHANE (3,3)  
**Item Number:** 30-3365  
**Lot Number:** C179147  
**Mfg. Date:** 07/01/2016  
**Expiration:** 07/13/2018

<table>
<thead>
<tr>
<th>Test</th>
<th>Specifications</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Point</td>
<td>164-168 °C</td>
<td>168 °C</td>
</tr>
<tr>
<td>Arsenic</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td></td>
<td>&lt;=1 ppm</td>
<td>None Detected</td>
</tr>
<tr>
<td>Cadmium</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td></td>
<td>&lt;=1 ppm</td>
<td>None Detected</td>
</tr>
<tr>
<td>Chromatographic purity</td>
<td>=&gt;98 %</td>
<td>99.7 %</td>
</tr>
<tr>
<td>Coliform</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td></td>
<td>&lt;=10 CFU/GM</td>
<td>None Detected</td>
</tr>
<tr>
<td>Description</td>
<td>pass</td>
<td>Off white, Crystalline powder</td>
</tr>
<tr>
<td>E. coli</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td></td>
<td>&lt;=10 CFU/GM</td>
<td>None Detected</td>
</tr>
<tr>
<td>Identification</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td>Lead</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td></td>
<td>&lt;=1 ppm</td>
<td>None Detected</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>&lt;=1.0 %</td>
<td>0.18 %</td>
</tr>
<tr>
<td>Mercury</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td></td>
<td>&lt;=1 ppm</td>
<td>None Detected</td>
</tr>
<tr>
<td>S. aureus</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td></td>
<td>&lt;=10 CFU/GM</td>
<td>None Detected</td>
</tr>
<tr>
<td>Salmonella</td>
<td>pass</td>
<td>Absent</td>
</tr>
</tbody>
</table>

*OFF-WHITE TO CREAM COLOR POWDER OR CRYSTALLINE POWDER; TURNS DARK BROWN IN PRESENCE OF LIGHT (IF RED COLOR BECOMES APPARENT, IT IS INDICATION OF DEGRADATION, PRODUCT MAY HAVE HAD PROLONGED EXPOSURE TO LIGHT).*
THANK YOU

Questions from the Committee?
Response to FDA review of benefits from intranasal VIP

Ritchie Shoemaker MD; CRBAI
Dennis Katz, RP; Hopkinton Drug
11/3/2016
Intranasal VIP safely corrects proteomic, transcriptomic abnormalities and resolves grey matter nuclear atrophy

- 2013 paper in Health relies on case definition of US GAO

- Statistically significant improvement, durable without adverse effects over 18 months: no other variable changed to disprove systemic benefit of VIP

- 2016 paper shows dramatic results of VIP use corrected transcriptomic abnormalities, especially in ribosomal and mitochondrial gene expression

- Study on 39 patients shows correction of grey matter nuclear atrophy to equal controls
Characteristics of compounded VIP Nasal Spray – 1

- 500 mcg/ml solution in sterile saline with 1% glycerin to help preserve secondary structure and prevent protein aggregation.
- All glassware and equipment used in preparation of spray disinfected with 70% isopropanol before use and rinsed with saline.
- Multiple HPLC stability studies confirm VIP nasal spray is highly stable with API maintaining correct amino acid sequence.
Characteristics of compounded VIP Nasal Spray – 2

- Highly stable pH of final product (6.1-6.2) is conducive to stability of the peptide given the predicted pI of VIP (9.82) and suitable for use as a nasal spray
- Despite multiple successful stability studies up to 90 days, dispensed with 60 day BUD to protect against poor patient compliance w/ handling/storage
- Compliant with applicable USP monographs regarding packaging (nasal sprayer) and residual solvent levels
History of compounded VIP in US

- Hopkinton Drug created VIP 500 mcg/mL in sterile saline
- First used 11/2008. Prescribers see great benefits (survey.)
- Life saving; quality of life restoration.
- pH ~6.15
- Manufactured to 98.8% purity
- No evidence of any cytokine release syndrome with use
- Nothing to support antidrug antibody issues (ADA)
Current use in US

- Total patients on VIP = 1710
- Total physicians prescribing = 314
- Individual refills = 1112
- Total fills = 7909
- Known cessation of use of VIP due to adverse effects = 5
Concern re peptide immunogenicity

Guidance for Industry 8/14

- Acute use reduces dyspnea, SOB, joint pain
  - No cytokine release syndrome
- Best use in HLA DRB1-4; DQ-3, DRB4-53
  - No evidence undesirable antibody responses
- In activated immune system illness: NO augmented responses
- Intranasal delivery increases risk of IG; but LESS IG is seen
- Use corrects autoimmunity; Ex: ACLA, ANCA
Chronic use

- Duration over 6 months rare
- Downwards titration over time (not increasing)
- Pulmonary hypertension markedly improved
- Exercise tolerance better
- Executive cognitive function better
Transcriptomics

- Anti-inflammatory
- Corrects massive mitochondrial gene activation
- Corrects ribosomal genes as well
- Corrects granzymes
- Corrects defensins
- Activates Ikaros
Results -2: % in 20 regions for duration

<table>
<thead>
<tr>
<th>Duration</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
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<tbody>
<tr>
<td>0-12 weeks</td>
<td>16</td>
<td>57</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>N = 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-24 weeks</td>
<td>12</td>
<td>42</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>N = 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;24 weeks</td>
<td>13</td>
<td>17</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>N = 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results -3: % found in 20 regions by dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>0-5</th>
<th>6-12</th>
<th>13+</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>15</td>
<td>12</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>0</td>
<td>55</td>
<td>42</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>22</td>
<td>35</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>21</td>
<td>21</td>
<td>4</td>
</tr>
</tbody>
</table>
## AN sorted by duration

<table>
<thead>
<tr>
<th>Duration</th>
<th>AN before</th>
<th>AN after</th>
<th>N=</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 weeks</td>
<td>3.5</td>
<td>2.8</td>
<td>15</td>
</tr>
<tr>
<td>13-24 weeks</td>
<td>3.4</td>
<td>1.9</td>
<td>11</td>
</tr>
<tr>
<td>&gt;25 weeks</td>
<td>3.6</td>
<td>0.9</td>
<td>4</td>
</tr>
</tbody>
</table>

Control AN = 0.9
# AN sorted by doses per day

<table>
<thead>
<tr>
<th></th>
<th>AN before</th>
<th>AN after</th>
<th>N=</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>2.8</td>
<td>2.6</td>
<td>15</td>
</tr>
<tr>
<td>8-12</td>
<td>3.1</td>
<td>1.6</td>
<td>11</td>
</tr>
<tr>
<td>&gt;13</td>
<td>3.9</td>
<td>0.9</td>
<td>4</td>
</tr>
</tbody>
</table>

- **Control AN = 0.9**
Response to recommendations-1

- 1. Stable in solution; nothing to suggest ADA
- 2. So-called severe immune adverse effects not supported in literature; not supported by 8 years and 1700 patients using drug
- 3. Three studies on VIP show safety and efficacy without adverse effects
Response to recommendations-2

- Given VIP accumulation in brain and positive effects on Ikaros, resolution of grey matter nuclear atrophy has never been seen before
- 4. Historical use continues to grow as the same safety and efficacy seen beginning in 2008 continues to this day
- Based on four criteria above, criteria weigh heavily to adding VIP to 503A Bulks List