

Tab D 1

Nonprescription Drug Manufacturers Association

Hydroquinone Task Group

Voluntary Labeling Guidelines
May 1992

The manufacturers and distributors of 2% hydroquinone-containing OTC skin discoloration fade [or lightening] products have independently decided to further assure proper use of these products.

These guidelines represent a combination of labeling language proposed by the Food and Drug Administration and new language defined independently by the industry members of the NDMA Hydroquinone Task Group. The result is a comprehensive label that takes into account all aspects of product application and thus helps to ensure safe and effective use of OTC skin discoloration lighteners.

Key aspects of the new guidelines include directions to consumers to:

1. Apply a small amount as a thin layer only to affected areas of dark brownish skin discoloration;
2. Discontinue use after the discoloration is gone;
3. Apply only again if the discoloration reappears;
4. Stop use if any skin irritation becomes severe or any darkening persists;
5. Do not use with other topical products containing resorcinol, phenol, or salicylic acid.
6. Do not apply to inflamed or broken skin;
7. Test overnight on a small section of their skin inside their elbow, if their skin is sensitive.

The use of the word, "discoloration," in the description of these products (e.g., skin discoloration lightener or skin discoloration fade cream) emphasizes that the use of these products is intended only on affected areas of skin discoloration. References to skin tone, even color, or moisturizing must be in the context of limited areas of over pigmentation.

Under this voluntary guideline, manufacturers and distributors would also comply with other general labeling pro-

(Continued . . .)

visions developed under the OTC Review as well as pertinent Voluntary Codes and Guidelines of the Nonprescription Drug Manufacturers Association.

Appended to this guideline are the following:

- A. Sample Label "A" of the Voluntary Guideline: Combination Products Containing 2% Hydroquinone and a Sunscreen
- B. Sample Label "B" of the Voluntary Guideline: Single Ingredient Products Containing 2% Hydroquinone

These sample labels are intended as examples only. Format and content changes that may be permitted under the regulations pertaining to the marketing of OTC products under the OTC Review will apply for participants in this voluntary industry program.

CONSUMER AFFAIRS

**Statement of Mark Green
Commissioner of Consumer Affairs
The City of New York**

**MARK GREEN
COMMISSIONER**

**Over-The-Counter Drug Feedback Meeting
Office of Over-The-Counter Drug Evaluation
Food and Drug Administration
May 20, 1992**

**The Safety of Skin Bleach Products for
Over-The Counter Human Use**

Dear Representatives of the FDA Monograph Review Staff:

I am pleased to see the FDA and the manufacturers address the issue of safety in skin bleach creams, and I am grateful that the consumers' viewpoint can be heard on this important discussion. As you know, the New York City Department of Consumer Affairs recently published a report on the safety and labelling claims of skin bleach products.

I hope the FDA will carefully consider all scientific data in determining whether or not hydroquinone should remain on the market, and if so for what use, and with what labelling. American consumers depend on you for our health and safety, state and local offices like the New York City Department of Consumer Affairs defer to your expertise.

Our report cited several studies which questioned the safety of bleach creams. One of the most important studies was issued by the National Toxicology Program (NTP). This study found, under the conditions of 2-year gavage studies, some evidence of carcinogenic activity of hydroquinone in some rats and mice.

Other studies in reputable medical journals cited cases of patients who used hydroquinone and suffered from exogenous ochronosis. Since you are no doubt familiar with these studies, I will not recite their findings now, but instead, make this information available for the record.

It was not the intent of our study to document cases of consumers who suffered from adverse effects of hydroquinone. However, in the course of our study, a customer representative of a skin bleach manufacturer advised an investigator posing as a consumer to avoid extended use of these products because she had received calls from other consumers who had suffered adverse effects from use.

In addition, when we issued our report, skin bleach cream users concerned about the safety of hydroquinone contacted our office. These consumers asked specific, fundamental questions concerning the safety of these products, questions for which we now cannot obtain the answers.

One woman who had seen a news report about our study on television, called to say that she knew three women who had exogenous ochronosis. She was glad that our report was released to the public because in her view, few women would make the connection between this side effect and use of the bleach cream. Other consumers who had used the cream contacted us because they are frightened of the possibility of adverse effects. They want to know-- and have the right to know-- the level of risk involved with use.

Another consumer wrote to us complaining about symptoms of exogenous ochronosis and asking for more safety information. She said, "I have been using these creams for twenty-five years, believing that the products were safe for general skin care and maintenance...In 1986 I developed a condition of unsightly patches and recurring blemishes which have since left permanent marks...I am still an avid user...I am unable to afford costly medical treatment."

As the FDA evaluates the safety of products containing hydroquinone, we must consider the interests of consumers first who too often do not have the information to make informed decisions, too often do not have the resources to make the appropriate complaints, and too often suffer in silence from the adverse effects of these products.

We urge the FDA to complete the evaluation of these skin bleach products promptly. Especially when corroborating studies exist raising consumer questions about safety, the burden of proof for a non-essential product should be on the company to prove it safe, not on the consumer-as-guinea-pigs to prove it unsafe. If the safety of these products cannot be determined immediately, then these products should be seized and banned.

Articles linking skin bleach creams containing 2% or less HQ to exogenous ochronosis in the United States. More articles have been written, but were not cited in the Consumer Affairs report.

1. "Exogenous Ochronosis in a Mexican-American Woman," Howard, *Cutis*, March 1990, p. 45. Woman used Esoterica and got exogenous ochronosis. "Our case adds to the growing number of reports of exogenous ochronosis resulting from the use of over-the counter hydroquinone-containing bleaching creams... ***the increasing number of reports of patients experiencing exogenous ochronosis due to bleaching creams containing 1 to 2 percent hydroquinone, used in several cases for less than six months, further demonstrates that this potential side effect of over-the-counter hydroquinone creams is real.***" [Italics added.]

2. "Exogenous Ochronosis in the United States," Lawrence, et.al., *Journal of the American Academy of Dermatology*, May, 1988, pps. 1207-11. Two women who used bleach creams with 1% hydroquinone got exogenous ochronosis. One woman had used the product for two to three months, the other for two to three years. The authors cited other experts who had ***"questioned the safety of 2% hydroquinone creams because their patients had acquired exogenous ochronosis."*** [Italics added.]

3. "Hyperpigmentation Following the Use of Bleaching Creams," Connor, *Archives of Dermatology*, January 1987, pg. 105. Conner noted the following: "Bleaching creams containing hydroquinone are widely used by black individuals in an attempt to 'brighten' or lighten the complexion. Although these products may be effective initially at lightening the skin, with long-term use, they may cause hyperpigmentation.... Although at first it was believed that only high concentrations of hydroquinone (>2%) were likely to cause localized exogenous ochronosis, ***similar findings may be seen in patients who have used 2% hydroquinone creams for several years.*** In most instances, the hyperpigmentation will fade dramatically over a period of years if the bleaching agent is discontinued. In severe cases, especially if papular lesions are present, the condition may be irreversible." [Italics added.]

4. "Hydroquinone-Induced Localized Exogenous Ochronosis Treated with Dermabrasion and CO2 Laser" Drs. Diven, et. al., *Journal of Dermatology, Surgery, and Oncology*, November 1990. p. 1018. Besides the quote in the attached letter, they wrote:

"The use of bleaching creams is practiced throughout the world. Many such creams are available in the United States, most of which are over-the-counter products. An ironic complication of hydroquinone-containing creams is the gradual deposition of pigmented fibers in the dermis. This produces a localized blue-black sooty pigmentation of the skin and in some instances, black colloid milia and papulonodules. Most cases have been partially or totally irreversible. We report cases of hydroquinone-induced exogenous ochronosis..."

5. "Hydroquinone-induced Ochronosis - Light and Electron Microscopic Features" Tidman, *Clinical Experimental Dermatology* Vol. 11, 1986, pps. 224-228.

6. "Ochronosis-like Pigmentation from Hydroquinone Bleaching Creams in American Blacks", Howshaw, *Archives of Dermatology*, 1985, Vol.121, pps. 105-108.

7. "Probable coexisting exogenous ochronosis and mercurial pigmentation managed by dermabrasion," Lang, *Journal of the American Academy of Dermatology*, November 1988, p. 942. "Long term use of bleaching creams may lead to a gray or blue-black discoloration of the skin. Creams containing mercury or hydroquinone may be responsible. The patient described in this report had used for many years bleaching creams containing both these agents....The patient was warned of the potential consequences of long-term use of hydroquinone-containing bleaching creams."

8. "Localized Exogenous Ochronosis" Dr. D. Cullison, *Journal of the American Academy of Dermatology*, Vol. 8, 1983 pps. 882-889. "Bleaching creams containing hydroquinone are modestly effective and generally safe...This patient's problem expands the arena for exogenous ochronosis due to hydroquinone bleaching creams from South Africa and emphasizes that *the safety of a hydroquinone preparation may not be ascertainable solely by concentration, but also requires consideration of the amount, frequency, and vigor of application.*" [Italics added.]

9. Letter from Professor Summers, Head, School of Pharmacy Medical University of Southern Africa to the FDA, December 15, 1988. Obtained from the FDA under the Freedom of Information Act. "In terms of the above document, [Tentative Final Monograph: Skin Bleaching Products for O-T-C Human Use]: "Since the tentative monograph was published however, a number of papers have appeared in the literature *which indicate that the allowed concentrations [i.e., 2%] of hydroquinone are not safe...*In view of these papers and a number of others which describe leucoderma as a consequence of the use of skin bleaching preparations, *would it not now be advisable to reconsider the whole monograph, more especially the use of hydroquinone as the active ingredient?.*"

The following articles have been written linking exogenous ochronosis and bleach creams containing more than 2% hydroquinone:

1. "Exogenous ochronosis and pigmented colloid milium from hydroquinone bleaching creams" Findlay, *British Journal of Dermatology* 1975 93, p 613. A study of thirty-five cases of exogenous ochronosis in South African women.

2. "Chronic Hydroquinone Poisoning of the Skin from Skin-Lightening Cosmetics: A South African Epidemic of Ochronosis of the Face in Dark-Skinned Individuals" Findlay, *South*

African Medical Journal, 1980 Vol. 57 p.187.

3. "Skin disorders in Black South Africans: A survey of 5000 patients seen at Ga-Rankuwa Hospital, Pretoria" Schulz, *South African Medical Journal*, 1982: 62: pps. 864-867. Skin damage resulting from the use of bleaching creams responsible for 6% of all skin disorders.

The following articles show exogenous ochronosis linked to skin bleach creams in South Africa after no more than 2% was allowed by law:

1. "Exogenous Ochronosis: an Epidemiological Study" N. Hardwick, *British Journal of Dermatology* 1989, vol.120, pps. 229-238. 15% of males and 42% of females were found to have exogenous ochronosis, with the prevalence amongst users of skin lighteners at 69% at two South African Hospitals.

2. "The melanocyte: An Essential Link in Hydroquinone Induced Ochronosis" Hull, *Journal of the American Academy of Dermatology*, March 1990. vol. 22 no.3 p. 529.

3. "Ochronosis in Black South Africans Who Used Skin Lighteners" Phillips, *American Journal Dermatopathy* vol. 8, pps.14-21.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Director
Monograph Review Staff (HFD-810)

SUBJECT: Material for Docket No. 78N-0065

TO: Dockets Management Branch (HFA-305)

- The attached material should be placed on public display under the above referenced Docket No.
- This material should be cross-referenced to Comment(s) No. _____.



William E. Gilbertson, Pharm. D.

Attachment