

JERUSSI CONSULTING, INC.

3311 Midland Road
Fairfax, Virginia 22031 USA

Tel: 703-273-3903 • Fax: 703-293-9161

January 16, 2004

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20857

Docket No. 2003P-0365

Dear Madame or Sir:

Attached are our comments in response to a November 13, 2003 letter to this docket submitted by Galderma, USA in which the latter commented on our suitability petition concerning its drug product Solage containing 2% Mequinol and 0.01% Tretinoin, NDA 20-922. Please make these comments part of the file.

Sincerely,

Robert A. Jerussi

Robert A. Jerussi, Ph.D.

2004 01 16 11:27

2003P-0365

C2

REBUTTAL LETTER

RE: Suitability Petition #2003P-0365 Letter of Opposition Filed on behalf of Galderma Labs. November 14th, 2003

In response to the letter of opposition to "Citizen" (Suitability) petition No. 2003P-0365 filed on behalf of Galderma Laboratories on November 14th, 2003 for substitution of one of the two active ingredients, Mequinol 2

% with a known equivalent strength of the precursor to mequinol, hydroquinone at 4% and permitting the product to be filed as a abbreviated New Drug Application, herewith, Jerussi Consulting files the following counter response to the claims made by Galderma against 4% w/w hydroquinone as a equivalent substitution for 2% mequinol in their product Solagè (#20-922) as follows:

1. Hydroquinone has a long and significant history as a safe and effective skin bleaching agent working on the mechanism of inhibiting the formation of melanin pigment with melanocytes located in the dermal basal area. 4-methoxy-phenol (4-hydroxy-anisol) has been demonstrated to act by the same mechanism, albeit, at the same range of penetration with the more lipid solubility resulting from the methoxylation. The propensity of products using hydroquinone as a single active or in combination with other active and purportedly active ingredients attests to this safety and effectiveness.
2. The evidence for a different toxicological profile between Mequinol and Hydroquinone is not substantiated for topical application by the references cited where the route of administration for the two active pharmaceutical ingredients were not compared by the same routes systemically. And NOT topically. Further LD₅₀ from oral gavage are not substantial indicators of chronic or even subacute toxicological effects. In contrast to the opposition letter from Galderma Labs, the references (*Ref 1 and Ref 2*) of the letter from Galderma, indeed, suggest the mechanism of acute oral toxicity of the two substances act by the same mechanism of action when administered systemically. Their evidence is further flawed by the lack of compliance with regulations for the research reports recited.
3. The *reference 3* (Nair and Tramposch, 1991) they refer to regarding a different mode for depigmentation was a not a conclusive finding nor a finding that was confirmed by subsequent research.
4. Occlusive patch testing referenced (*reference 4*). Since the formulations were different in the study to the marketed product and the irritation measurements were subjectively made and scored, these results can not be used in any manor to support the author's claims. Further,

Occlusion testing, can add significant variations to dermal scoring for various actives beyond the ones reviewed here. Occlusion of the treated area is not the recommended for the *Reference Listed Drug*, (RLD), Solagè.

5. Galderma cites the triple combination product of theirs Tri-Luma® Cream as the only combination product containing tretinoin and hydroquinone in the list as not being equivalent because of the presence of the corticosteroid fluocinolone acetonide, and further, suggest the corticosteroid is responsible for a very small reduction in minor adverse events. Reviewing the data presented presents the pharmacological dilemma of describing a "novel" mechanism of action for corticosteroids "desquamation" at the application site.

Further Galderma Laboratories fails to point out that the (tretinoin) retinoic acid in their product "Tri-Luma®" is (5) five times higher than that for their product "Solagè". This fact in itself is substantial when consider the equivalency of the two active ingredients, mequinol and hydroquinone from a view of safety.

I conclude based on the lack of substantial opposition in the November 14th, 2003 letter from Galderma USA that this petition, 03P-0365 be allowed.