DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 13 2000

TRANSMITTED VIA FACSIMILE

Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs
Johnson & Johnson Consumer Companies, Inc.
199 Grandview Road
Skillman, NJ 08558-9418

Re: NDA 19-963
Renova (tretinoin emollient cream) 0.05%
MACMIS# 9192

Dear Dr. Wille:

As part of our routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of a direct-to-consumer (DTC) journal advertisement for Renova (tretinoin emollient cream) 0.05%, disseminated by Johnson and Johnson Consumer Companies, Inc., (J&J) that is in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Specifically, we refer to a journal advertisement (04DD3480B) for Renova that appears in the July/August, 2000 issue of *Martha Stewart Living*. We object to your dissemination of this advertisement for the following reasons:

Misleading Efficacy Claims

"Before I even have to think about a face lift, I'm thinking Renova."

J&J presents this header with a picture of a woman's face and with the prominent sub-headers, "Only Renova is approved…to reduce fine wrinkles" and "Renova actually changes your skin." These headers and the picture are presented prominently while the actual indication and limiting information is presented in a non-prominent manner. Thus, the overall presentation misleading implies that Renova is more effective than demonstrated.

For example, J&J does not prominently present that Renova must be used in conjunction with a comprehensive skin care & sun avoidance program. In fact, the approved product labeling (PI) states that many patients achieve desired effects on fine wrinkling with the use of comprehensive skin care and sun avoidance programs and emollient creams NOT containing tretinoin. Also, the information that Renova does not eliminate wrinkles,

repair sun damaged skin, reverse photo-aging or restore a more youthful skin is not prominently presented. Instead this information is presented in running text without any emphasis in comparison to the more prominent headers.

J&J states that Renova is "so effective" and "it's where the search for a truly effective wrinkle cream stops." These claims are misleading because they overstate the efficacy. In the clinical trials, the majority of patients had minimal or no improvement. We note that J&J presents the efficacy rates in tiny print under the "before" and "after" pictures. However, this efficacy information is minimized and difficult to read as compared to the more prominent benefit claims.

Further, J&J presents Renova's effect on "crow's feet" in a prominent header but does not include the indication information from the PI that Renova has demonstrated no mitigating effect on significant signs of chronic sun exposure such as coarse or deep wrinkling.

Unsubstantiated Superiority Claim

"Because it's the only prescription cream approved by the FDA, it's a step beyond cosmetic wrinkle creams."

This claim is misleading because it suggests that Renova is better than other products without substantial supporting evidence.

Action Requested

You should immediately cease distribution of the journal advertisement and all other promotional materials for Renova that contain the same or similar claims or presentations cited in this letter. You should submit a written response to us, on or before October 27, 2000, describing your intent and plans to comply with the above. In your letter to us, you should include a list of all promotional materials that were discontinued, and the discontinuation dates.

You should direct your response to me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official. In all correspondence regarding

this particular submission, please refer to MACMIS ID# 9192 in addition to the NDA number.

Sincerely,

/S/

Cheryl Y. Roberts
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

At some point you may consider having a face lift. But before you have to think about that, think RENOVA.

ONLY RENOVA IS APPROVED BY THE FDA TO REDUCE FINE WRINKLES.

"Cosmetic creams alone may be enough for some people. But not for me. And I'm not ready to think about cosmetic surgery yet. But right now, I've found something that works to really reduce my fine wrinkles, even fade brown spots. RENOVA. And because it's the only prescription cream approved by the FDA, it's a step beyond cosmetic wrinkle creams."

RENOVA ACTUALLY CHANGES YOUR SKIN.

"The way my dermatologist explained it is that RENOVA is a rich emollient cream whose active ingredient is a unique Vitamin A derivative like the one that naturally occurs in your body. She said that researchers think the reason RENOVA is so effective is because they believe it works deep at the cellular level. In effect, RENOVA physically changes your skin.

"She also assured me that RENOVA has been rigorously tested for safety and effectiveness. And while it will not repair sun damaged skin, totally eliminate wrinkles or reverse the aging process, it is clinically proven to reduce fine wrinkles, even fade brown spots, when used as part of a skincare program that includes your moisturizer and sun protection."

ASK YOUR DERMATOLOGIST IF RENOVA IS RIGHT FOR YOU.

If cosmetic creams, including sunscreens and moisturizers, haven't given you the results you want, ask your dermatologist about adding RENOVA. RENOVA is not appropriate for everyone, so talk to your dermatologist if you're on other medications, pregnant or nursing. See attached information for more on who should or shouldn't use RENOVA. Results of use beyond 48 weeks have not been established in controlled clinical trials. Clinical trials in those over 50 or with moderately or heavily pigmented skin have not been conducted.

When you use RENOVA, you can expect to experience some redness, itching or flaking because RENOVA is a skin irritant. This is most often mild, and most common when treatment is started. Remember to limit your time in the sun and always wear a sunscreen.

All before-after photographs are completely unretouched. Results are after 24 weeks treatment with RENOVA and a total skin care program, including sun protection.

FINE WRINKLES AND CROW'S-FEET

Photo represents minimal improvement. 64% of patients experienced either minimal(40%) or moderate(24%) improvement. 36% experienced no improvement.

BROWN SPOTS

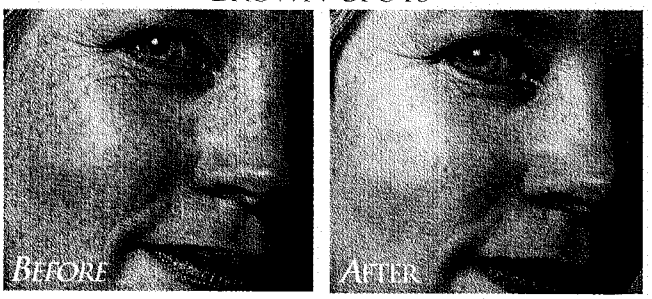
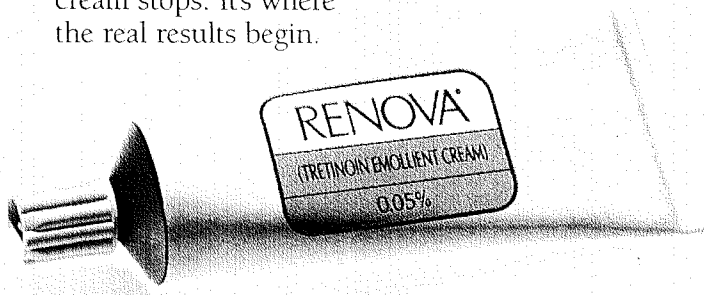


Photo represents moderate improvement. 65% of patients experienced either moderate(38%) or minimal(27%) improvement. 35% experienced no improvement.

For your free information kit plus savings, visit us at www.thinkrenova.com. Or call 1-888-689-9023. It's where the search for a truly effective wrinkle cream stops. It's where the real results begin.



www.thinkrenova.com
1-888-689-9023

RENOVA®
(tretinoin emollient cream) 0.05%

See following page for important information.

RENOVA®

(TRETINOIN EMOLLIENT CREAM)

0.05%

FOR TOPICAL USE ON THE FACE ONLY

Brief Summary

RENOVA (tretinoin emollient cream) 0.05% contains the active ingredient tretinoin (a retinoid) in an emollient cream base.

IMPORTANT NOTE — This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

INDICATIONS AND USAGE:

RENOVA (tretinoin emollient cream) 0.05% is indicated as an adjunctive agent (see second bullet point below) for use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin in patients who do not achieve such palliation using comprehensive skin care and sun avoidance programs alone (see bullet point 3 for populations in which effectiveness has not been established). **RENOVA DOES NOT ELIMINATE WRINKLES, REPAIR SUN DAMAGED SKIN, REVERSE PHOTO-AGING, or RESTORE A MORE YOUTHFUL or YOUNGER DERMAL HISTOLOGIC PATTERN.** Many patients achieve desired palliative effects on fine wrinkling, mottled hyperpigmentation, and tactile roughness of facial skin with the use of comprehensive skin care and sun avoidance programs including sunscreens, protective clothing, and emollient creams **NOT** containing tretinoin.

- RENOVA has demonstrated NO MITIGATING EFFECT on significant signs of chronic sun exposure such as coarse or deep wrinkling, skin yellowing, lentigines, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.
- RENOVA should only be used under medical supervision as an adjunct to a comprehensive skin care and sun avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing when desired results on fine wrinkles, mottled hyperpigmentation, and roughness of facial skin have not been achieved with a comprehensive skin care and sun avoidance program alone.
- The effectiveness of RENOVA in the mitigation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin has not been established in people greater than 50 years of age OR in people with moderately to heavily pigmented skin. In addition, patients with visible actinic keratoses and patients with a history of skin cancer were excluded from clinical trials of RENOVA. Thus the effectiveness and safety of RENOVA in these populations are not known at this time.
- Neither the safety nor the effectiveness of RENOVA for the prevention or treatment of actinic keratoses or skin neoplasms has been established.
- Neither the safety nor the efficacy of using RENOVA daily for greater than 48 weeks has been established, and daily use beyond 48 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See **WARNINGS** section.)

CONTRAINDICATIONS:

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS:

- RENOVA is a dermal irritant, and the results of continued irritation of the skin for greater than 48 weeks in chronic, long term use are not known. There is evidence of atypical changes in melanocytes and keratinocytes, and of increased dermal elastosis in some patients treated with RENOVA for longer than 48 weeks. The significance of these findings is unknown.
- Safety and effectiveness of RENOVA in individuals with moderately or heavily pigmented skin have not been established.
- RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided or minimized during use of RENOVA. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using RENOVA. Patients with sunburn should be advised not to use RENOVA until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using RENOVA and assure that the precautions outlined in the Patient Package Insert are observed.

RENOVA should be kept out of the eyes, mouth, angles of the nose, and mucous membranes. Topical use may cause severe local erythema, pruritus, burning, stinging, and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with utmost caution in patients with this condition.

Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, or discomfort may occur.

PRECAUTIONS:

General: RENOVA should only be used as an adjunct to a comprehensive skin care and sun avoidance program. (See **INDICATIONS AND USAGE** section.)

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of RENOVA should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using RENOVA.

Information for Patients: See Patient Package Insert.

Drug Interactions: Concomitant topical medications, medicated or abrasive soaps, shampoos, cleansers, cosmetics with a strong drying effect, products with high concentrations of alcohol, astringents, spices or lime, permanent wave solutions, electrolysis, hair depilatories or waxes, and products that may irritate the skin should be used with caution in patients being treated with RENOVA because they may increase irritation with RENOVA.

RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a life-time dermal study in CD-1 mice, at 100 and 200 times the average recommended human topical clinical dose, a few skin tumors in the female mice and liver tumors in male mice were observed. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when tretinoin was administered topically at a dose 5 times the average recommended human topical clinical dose. For purposes of comparisons of the animal exposure to human exposure, the "recommended human topical clinical dose" is defined as 500 mg of 0.05% RENOVA applied daily to a 50 kg person.

In a chronic, two-year bioassay of Vitamin A acid in mice performed by Tsubura and Yamamoto, generalized amyloid deposition was reported in all groups in the basal layer of the Vitamin A treated skin. In CD-1 mice, a similar study reported hyalinization at the treated skin sites and the incidence of this finding was 0/50, 3/50, 3/50, and 2/50 in male mice and 1/50, 0/50, 4/50, and 2/50 in female mice from the vehicle control, 0.25 mg/kg, 0.5 mg/kg, and 1 mg/kg groups, respectively.

Studies in hairless albino mice suggest that tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. In other studies, when lightly pigmented hairless mice treated with tretinoin were exposed to carcinogenic doses of UVB light, the incidence and rate of development of skin tumors were either reduced or no effect was seen. Due to significantly different experimental conditions, no strict comparison of these disparate data is possible at this time. Although the significance of these studies to humans is not clear, patients should minimize exposure to sun.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

Dermal Segment I and III studies with RENOVA have not been performed in any species. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (>400 times the average recommended human topical clinical dose).

Pregnancy:

Teratogenic effects: Pregnancy Category C.

ORAL tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. It was teratogenic and fetotoxic in rats when given orally in doses 1000 times the average recommended human topical clinical dose. However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which, metabolically, is closer to humans for tretinoin than the other species examined, fetal malformations were reported at doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (1000 times the average recommended human topical clinical dose), although increased skeletal variations were observed at all doses. A dose-related increased embryolethality and abortion was reported. Similar results have also been reported in pigtail macaques.

TOPICAL tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (200 times the recommended human topical clinical dose). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was dermally applied.

There are other reports in New Zealand White rabbits with doses of approximately 80 times the recommended human topical clinical dose of an increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species.

In contrast, several well-controlled animal studies have shown that dermally applied tretinoin was not teratogenic at doses of 100 and 200 times the recommended human topical clinical dose, in rats and rabbits, respectively.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin (Retin-A). Although no definite pattern of teratogenicity and no causal association has been estabiished from these cases, 5 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Non-teratogenic effects:

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered in doses 100 times the recommended topical human clinical dose. Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 500 times the recommended topical human clinical dose.

There are, however, no adequate and well-controlled studies in pregnant women. RENOVA should not be used during pregnancy.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RENOVA is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in patients less than 18 years of age have not been established.

Geriatric Use: Safety and effectiveness in individuals older than 50 years of age have not been established.

ADVERSE REACTIONS:

(See **WARNINGS** and **PRECAUTIONS** sections.)

In double-blind, vehicle-controlled studies involving 179 patients who applied RENOVA to their face, adverse reactions associated with the use of RENOVA were limited primarily to the skin. During these trials, 4% of patients had to discontinue use of RENOVA because of adverse reactions. These discontinuations were due to skin irritation or related cutaneous adverse reactions.

Local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus were reported by almost all subjects during therapy with RENOVA. These signs and symptoms were usually of mild to moderate severity and generally occurred early in therapy. In most patients the dryness, peeling, and redness recurred after an initial (24 week) decline.

OVERDOSAGE:

Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

Rx only.

DERMATOLOGICAL DIVISION
ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869

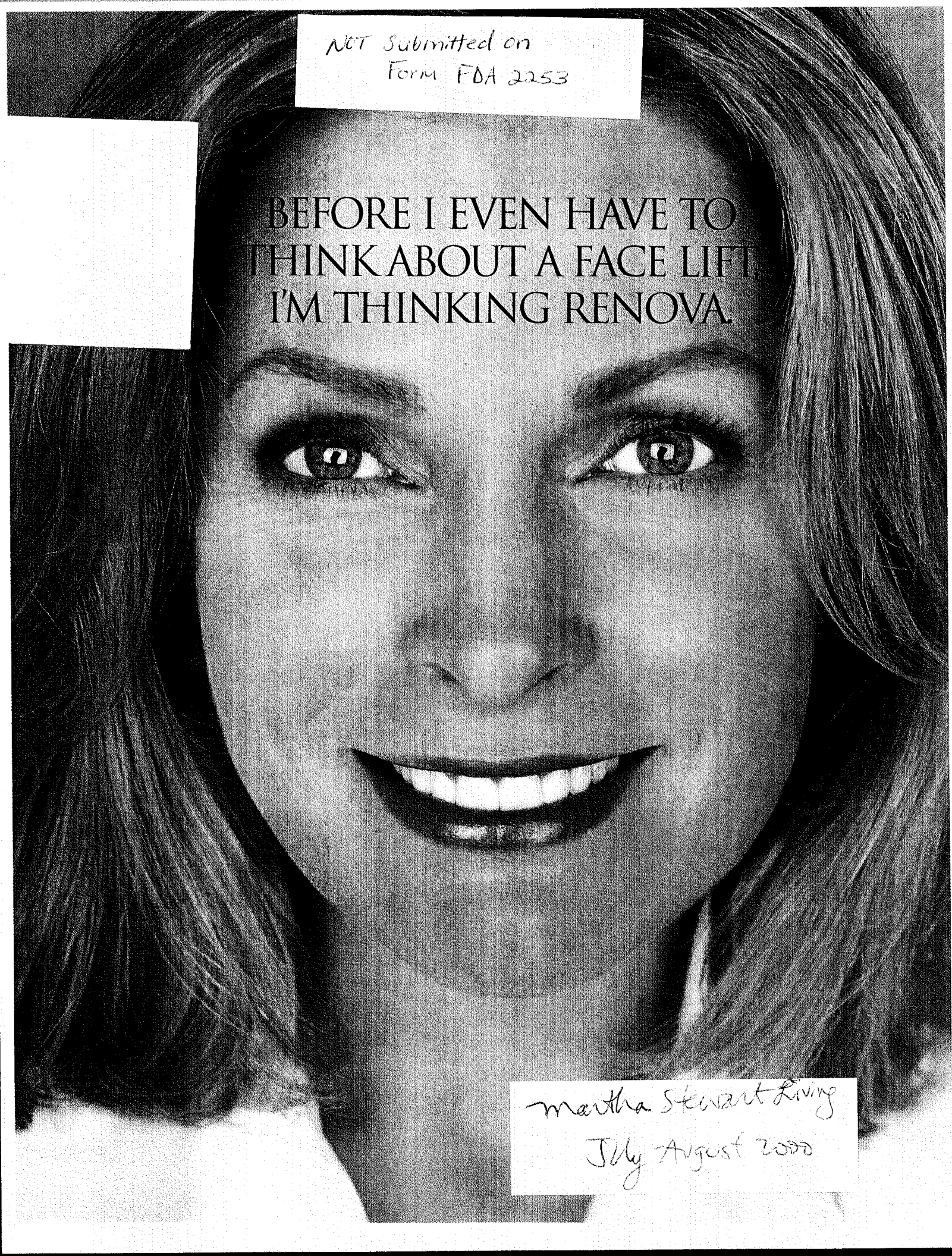
ORTHO

Revised February 1998

U.S. Patents 4,603,146, 4,423,041 and 4,877,805653-10-870-5B

Printed in USA

NOT Submitted on Form FDA 2253



Martha Stewart Living
July August 2000