

Evaluation of Efficacy of a Skin Care Regimen Containing Methyl Estradiolpropanoate (MEP) for Treating Estrogen Deficient Skin

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ABSTRACT

Background: Aging is a complex process due to the interplay of intrinsic factors (such as genetics and hormones) and extrinsic factors (including ultraviolet radiation and pollution). A significant cause of intrinsic aging in women is the loss of estrogen as a result of the onset of menopause.

Objective: A single site experience trial to assess the efficacy of Emepelle (Biopelle, Ferndale Pharma Group, Ferndale, MI), a skin care regimen containing Methyl Estradiolpropanoate (MEP)®, for the treatment of Estrogen Deficient Skin (EDS). The secondary objective was to assess patient tolerability and satisfaction.

Methods: Fourteen female subjects aged 53-68 years who were amenorrheic for 1-10 years (mean, 5 years), with at least a Grade II in Wrinkling (fine to moderate-depth wrinkles, moderate number of lines) and score of at least 5 (of 9; moderate-to-severe) in elastosis on the clinician-assessed Fitzpatrick-Goldman Classification of Wrinkling and Elastosis Scale, and a 3 or greater on the Investigator Facial Skin Hydration Scale, were included in the study. The subjects were instructed to apply the product Emepelle Serum in the morning, and the product Emepelle Night Cream in the evening to the entire freshly washed and dried face. Follow up visits were performed at 8 weeks, 14 weeks, and 20 weeks to evaluate efficacy and safety. Canfield Visia Complexion Analysis and standard photography was performed at baseline and at each follow up visit.

Results: On a 0-4 Facial Hydration Scale, 100% of study participants by week 20 showed at least one-grade improvement and 93% saw two grades or more improvement in hydration. 100% of study participants showed aesthetic improvements per investigator-assessed Global Aesthetic Improvement Scale (GAIS) at week 14. By week 20, 93% of study participants responded that the combination of Emepelle Serum and Night Cream regimen helped improve wrinkles, texture, and color, and 86% of study participants responded that Emepelle helped improve sun-damage, thickness, and integrity. In the Quality of Life questionnaire, 86% responded that Emepelle helped alleviate some or all of the skin issues they developed since entering menopause. Investigator clinical assessment scored patients with a 53% improvement in texture, 21% improvement in keratoses, and 15% improvement in laxity on the Alexiades-Armenakas Comprehensive Grading Scale for Assessment of Skin Aging and Photodamage by the end of the study at week 20.

Conclusions: Patients in the study indicated satisfaction with the formulations of Emepelle Serum and Night Cream. Younger patients showed significant improvement by about 8 weeks. For patients who have been in menopause longer, significant improvement was seen by week 20, suggesting MEP's potential ability to reactivate dormant estrogen receptors.

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INTRODUCTION

Aging is a complex process due to the interplay of intrinsic factors (such as genetics and hormones) and extrinsic factors (including ultraviolet radiation and pollution). A significant cause of intrinsic skin aging in women is loss of estrogen as a result of the onset of the menopause, with this change being referred to as Estrogen Deficient Skin (EDS). Women in menopause manifest characteristics of EDS with documented significant decrease in Collagen I and III and type 1 procollagen, decrease in glycosaminoglycan content, decrease in TGF-β1 expression, reduced expression of IGF-1 receptors and production of IGF-1, and reduced reactive oxygen species (ROS) defense activity, resulting in skin dryness, pruritis, increased wrinkles, thinning, atrophy, and impaired wound healing.[1] One of the ways to treat EDS in women is through oral hormone replacement therapy (HRT). While this therapy has many potential benefits, HRT was not specifically developed or recommended for cutaneous benefits and can possibly precipitate in some cases significant adverse events, including breast cancer or stroke.

Studies of postmenopausal women indicate that estrogen attenuation is associated with hot flashes as well as cutaneous dryness, atrophy, fine wrinkling, and poor healing. Epidermal thinning, declining dermal collagen content, diminished skin

moisture, decreased laxity, and impaired wound healing have all been characterized in reports on postmenopausal women.[2] Studies have shown a decrease in estrogen levels leads to a 30% loss of collagen in the first 5 years of menopause.[3] Estrogen has been found, at normal blood levels, to help retain and restore skin moisture through the promotion of sebum secretion, primarily by regulating the expression of insulin-like growth factor receptors and increasing the production of insulin-like growth factors from fibroblasts.[4] Women of menopausal age seek alternatives to HRT regimens that are linked with an increase in systemic estrogen. By creating a non-hormonal estrogen receptor activator (NERA), Ferndale Pharma Group has developed another approach to address aging in the estrogen deficient female. Emepelle (Biopelle, Ferndale Pharma Group, Ferndale, MI) is a new category of skin care. The signature ingredient, Methyl Estradiolpropanoate (MEP), is not a hormone. It is specifically a non-hormonal compound that can activate estrogen receptors on skin cells. Thus, MEP is an estrogen analog that activates the cutaneous estrogen receptor. Once that estrogen receptor activation takes place, the remaining compound has no further activity and is found to be an inactive metabolite.[5]

Methyl Estradiolpropanoate

Facial skin aging is accelerated in postmenopausal females due to decreased collagen, reduced hydration, and loss of skin elasticity constituting the characteristics of EDS. The presence of estrogen receptors on dermal fibroblasts and epidermal keratinocytes confirms the role of estrogen in skin health. A recent double-blind randomized pilot study evaluated the efficacy and tolerability of topical MEP as an anti-aging cosmeceutical with estrogen-like cutaneous effects in postmenopausal women who had never taken hormone replacement therapy (HRT). MEP was applied to the face twice daily for 14 weeks but was metabolized in the skin to an inactive compound avoiding estrogen side effects, as demonstrated by the safety study. The efficacy study investigator noted MEP induced statistically significant improvement from baseline at week 14 in dryness (P<0.001), laxity (P=0.001), atrophy (P=0.003), and dullness (P<0.001) as compared to vehicle. Four of nine subjects in the biopsy sub study demonstrated an increase in fibroblast's estrogen receptor staining. The novel concept of a safe and efficacious soft estrogen facial cosmeceutical may provide appearance benefits for postmenopausal women.

The safety of topical MEP was demonstrated by the lack of active MEP and the presence of the carboxylic acid MEP inactive metabolite in the serum of subjects who had used the formulation for 12 weeks. This soft effect allowed targeted delivery of the MEP to the skin without systemic side effects. Restoration of estrogen-like skin effects might induce the production of collagen I, responsible for the strength of the skin, and collagen III, contributing to the elastic skin properties, while reducing the expression of matrixmetalloprotease 1 (MMP-1).[5]

Methyl Estradiolpropanoate (MEP) is a synthetic estrogenic sterol ester, which has been shown to have estrogen-like cutaneous effects but is metabolized in the skin to an inactive compound, thus avoiding estrogen side effects.[4] Emepelle skin care regimen consists of Emepelle Serum and Night Cream containing MEP that is applied to the face to specifically target estrogen deficient skin. This skincare line takes a multifactorial approach to treat both intrinsic aging and photoaging by including a number of other cosmeceutical agents.

Emepelle Serum

The Emepelle Serum is a fast-absorbing, oil-free formulation that can be layered with sunscreen or under makeup. The serum contains 1% MEP to help activate estrogen receptors in the skin[6,7] and is intended for use in either the morning, the evening, or both morning and evening.

The ingredient niacinamide helps induce collagen synthesis and reduce the signs of UV-induced skin aging. Topical niacinamide has shown significant skin appearance improvement effects for clinical signs of photoaging, hyperpigmentation, red blotchiness, and skin sallowness.[8] The formula also contains the antioxidants vitamin C, vitamin E, and ferulic acid, which help neutralize free radicals and prevent cell damage from UV radiation.[9,10,11] A blend of peptides helps combat oxidative stress and helps improve the appearance of fine lines, wrinkles, and skin laxity.[4] Hyaluronic acid helps hydrate and maintain the skin's moisture barrier.[12]

Night Cream

The key ingredients in Emepelle Night Cream include 2% MEP that helps to restore the natural function of estrogen deficient skin while utilizing the skin's natural nighttime repair activities. Retinol 0.1% and hydroxypinacolone retinoate 0.05% aid in nightly rejuvenation and stimulate the production of new blood vessels in the skin, which help improve skin color and reduce the appearance of wrinkles.[13] The niacinamide addresses skin tone and texture to help brighten and smooth the appearance of fine lines and wrinkles and provides additional antioxidant protection.[8] The inclusion of tetrapeptide-26, palmitoyl oligopeptide, and palmitoyl tetrapeptide-7 supports cell proliferation and helps combat oxidative stress[14]; and emollients and humectants help hydrate the skin and maintain its moisture barrier.

METHODS

An open-label study was designed to evaluate the efficacy and patient perception of Emepelle's skin care regimen containing MEP on treating Estrogen-Deficient Skin (EDS).

Fourteen female subjects aged 53-68 years (mean, 60 years) in generally good health who have been amenorrheic for at least 1

year and no more than 10 years were enrolled in the study. Each subject enrolled in the study had at least a Grade II in wrinkles and score of 5 (of 9) in elastosis on the Fitzpatrick-Goldman Classification of Wrinkling and Degree of Elastosis Scale, a validated assessment tool used to measure wrinkling and degree of elastosis including laxity, dyschromia, erythema, and changes in texture. Each subject enrolled also measured with a score of 3 or greater on the Facial Skin Hydration Scale.

Exclusion criteria included patients who were either currently on hormone replacement therapy, or had ever been treated in the past with hormone replacement therapy, patients using any topical cosmetic anti-wrinkle and/or skin lightening products known to affect skin aging or products containing vitamin A derivatives on the face within 14 days prior to or during the study period. In addition, women using any topical imiquimod, 5-fluorouracil, or diclofenac on their face within 12 weeks prior to or during the study period were also excluded. Subjects receiving a chemical peel, or a non-ablative laser or light-based therapy on their face must have had discontinued the specific treatment at least 3 months prior to entering the study. Subjects receiving radiofrequency or ultrasound treatment on their face must have had discontinued the treatment at least 6 months prior to entering the study. Subjects receiving traditional dermabrasion (deep skin peel) such as diamond fraise, and/or ablative laser treatments on their face must have had discontinued the treatment at least 6 months prior to entering the study. Patients with a history of or the presence of any skin condition/disease that might interfere with the diagnosis or evaluation of study parameters were also excluded. Other exclusion criteria were having current actinic keratoses or any skin cancer(s) in the treatment areas; significant history or current evidence of a medical, psychological or other disorder; prior history of cancer other than basal cell carcinoma (BCC); any active systemic disease that is not yet deemed medically stabilized; or an active bacterial, fungal, or viral infection.

Skin Care Regimen

Subjects were instructed at the baseline visit to apply one pump of the Emepelle Serum to face in the morning (immediately after cleansing and drying) and to apply a thin layer of Emepelle Night Cream to the entire face at night (immediately after cleansing and drying). Subjects were told to only use the skin care products provided and to wash their face twice daily with the provided gentle cleanser (CeraVe®). Each morning, subjects were required to apply the provided facial sunscreen SPF30 (CeraVe®) 15 minutes after applying the Emepelle Serum and to reapply the sunscreen every 2 hours throughout the day if exposed to direct sunlight.

Study restrictions included avoiding excessive exposure to sunlight or sunlamps in the treatment area and not applying any lotions, creams, powders, or solutions to the treated areas during the study period unless provided by their physician. Use of any topical products containing retinoids, hydroquinone, alpha-hydroxy acids, salicylic acid, and vitamins C or E on the face was also restricted for the duration of the study.

Follow up visits with photos were performed at 8 weeks, 14 weeks, and 20 weeks to evaluate efficacy.

Canfield Visia Complexion Analysis and standard photography were performed at baseline and at each of these follow up visits to capture ongoing and post-treatment status.

Quantitative Evaluations

Quantitative evaluations including validated Fitzpatrick-Goldman Classification of Wrinkling and Degree of Elastosis Scale, Alexiades-Armenakas Comprehensive Grading Scale for Assessment of Skin Aging and Photodamage, the Facial Skin Hydration Scale, a 0 to 5 scale where 0 = smooth and well-hydrated skin and 5 = severely dry skin with moderate scaling and coarseness, and Clinician Global Aesthetic Improvement Score (C-GAIS), a 1 to 5 scale, with 1 meaning very much improved and 5 meaning worsened, were performed to assess improvement in facial aging. Subject Qualify of Life Questionnaire and Subject Improvement Score evaluations were used to assess tolerability.

Investigator Evaluations

Investigator performed evaluations included the Fitzpatrick-Goldman Classification of Wrinkling and Degree of Elastosis Scale (0-9 scale) at Visit 1, 2, 3, and 4. A score of 0-4 using the Alexiades-Armenakas Comprehensive Grading Scale for (1) Rhytides, (2) Dyschromia, (3) Erythema-Telangectasia, (4) Keratoses, and (5) Texture. For each category, a mean percent improvement was calculated on Visit 1, 2, 3, and 4. The Facial Skin Hydration was used for evaluation on Visit 1, 2, 3, and 4. The Clinician Global Aesthetic Improvement Score (C-GAIS) was completed on Visit 2, 3, and 4. The Investigator Tolerability and Side Effects Assessment was completed at all follow-up visits to evaluate any side-effects including erythema, edema, scaling, and itching (0 to 4 scale where 0 = none and 4 = severe).

Subject Evaluations

The Subject Global Aesthetic Improvement Score (S-GAIS) was completed on Visit 2, 3, and 4. The Subject Quality of Life Questionnaire was completed by the patient on post-final treatment Visit 2, 3, and 4. The Subject Questionnaire on Quality of Skin Improvement was completed on treatment Visit 2, 3, and 4. The Subject Tolerability and Side Effects Assessment was completed at all follow-up visits (erythema, edema, scaling, and itching on a 0 to 4 scale where 0 = none and 4 = severe).

RESULTS

Fourteen subjects successfully completed the study.

Week 8

At week 8, 93% of patients felt that they were "more comfortable" with the appearance of their skin compared to baseline and 50% or more of the participants reported improvement in wrinkles, thickness, integrity, dullness, texture, and color. Also, at week 8, on the 0 to 5 Facial Skin Hydration Scale, 100% of study participants documented at least one grade improvement and 64% verified two grades or more improvement.

By week 8, subjects showed a 34% improvement in texture on the Alexiades-Armenakas Comprehensive Grading Scale for Assessment of Skin Aging and Photodamage. On the Subject Questionnaire on Quality of Life, 93% said their skin felt "more comfortable" post application of the topical products, that their skin "looked better".

Week 14

On a 0-5 Facial Skin Hydration Scale, 100% of study participants showed at least 1-step improvement and 8 of 14 (57%) saw a 2-grade or more improvement in hydration. 100% of study participants showed aesthetic improvements per Investigator Global Aesthetic Improvement Scale (GAIS) at week 14.

Baseline to Week 20

By week 20, 93% of study participants responded that Emepelle helped improve the appearance of wrinkles, texture, and color.

Also, by week 20, 86% of study participants responded that Emepelle helped improve the appearance of sun damage, thickness, and integrity. In the Subject Questionnaire on Quality of Life, 86% of study participants responded that Emepelle helped alleviate some or all of the skin issues they have developed since entering menopause by week 20.

Overall, from baseline to end of study at 20 weeks, patients showed a 53% improvement in texture, 21% improvement in keratoses, and 15% improvement in laxity on the Alexiades-Armenakas Quantitative and Comprehensive Grading Scale.

DISCUSSION

While all patients experienced at least a 1-step improvement in hydration on a 5-point scale at 8 weeks onward, more notable hydration improvements occurred throughout the course of the study. For example, at 8 weeks, only 7% of patients experienced a 3+ step improvement in hydration whereas at 20 weeks, 64% of patients experienced a 3+ step improvement in hydration.

More notable improvements were made in terms of appearance of the skin and menopausal-related skin issues throughout the course of the study. For example, at 8 weeks, 21% of patients reported 'very' or 'extremely' to the question "Do you feel the application of the study topical products made your skin look better" vs 64% after 20 weeks.

Furthermore, at 8 weeks, 7% of patients reported 'very' or 'extremely' to the question "Do you feel the study products have helped alleviate some or all of the skin issues you have developed since entering menopause" compared to 64% at 20 weeks.

Studies have shown that estrogen attenuation/diminution in postmenopausal conditions accelerates many skin changes, including dryness, atrophy, fine wrinkling, and poor wound healing.[15] Thus, the effects of low estrogen on the skin are an important endogenous cause of aging skin in women; yet, topical strategies that target estrogen deficiency are limited.[16]

In this open-label experience trial, all patients expressed satisfaction with the formulations of Emepelle Serum and Night Cream. Patients on the younger end of the study spectrum (53-60 years) seemed to show significant improvement in about 8 weeks (See Figures 1 and 2).

In older patients (over 63 years) who presumably have been in menopause longer, significant improvement seemed to take longer, but was shown by 20 weeks (See Figures 3 and 4).

Since a subset of older trial participants took longer for their roughness and dryness to improve, it may take time to rebuild

FIGURE 1. Fifty-three-year-old female patient at baseline and week 8 after morning use of Emepelle Serum and evening use of Emepelle Night Cream. *Photo Courtesy of Joel L. Cohen MD*

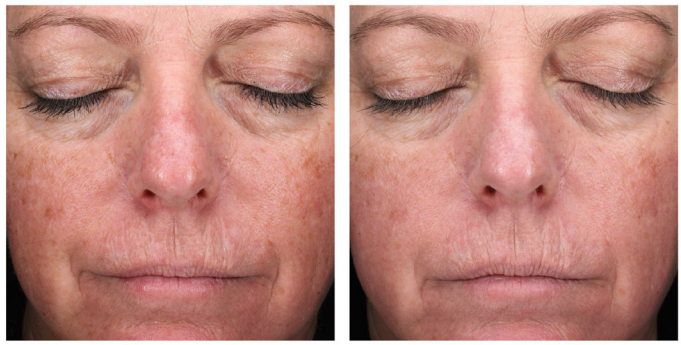

FIGURE 2. Sixty-year-old female patient at baseline and week 8 after morning use of Emepelle Serum and evening use of Emepelle Night Cream. *Photo Courtesy of Joel L. Cohen MD*

FIGURE 3. Fifty-three-year-old female patient at baseline and week 20 after morning use of Emepelle Serum and evening use of Emepelle Night Cream. *Photo Courtesy of Joel L. Cohen MD*

FIGURE 4. Sixty-three-year-old female patient at baseline and week 20 after morning use of Emepelle Serum and evening use of Emepelle Night Cream. *Photo Courtesy of Joel L. Cohen MD*

more estrogen receptors and turn the pathways back on. This suggests that the longer patients have been amenorrheic, the more of their estrogen receptors have been lost, or at least have become more dormant or down-regulated.

CONCLUSION

Facial skin aging in postmenopausal females is due to cumulative photodamage and other intrinsic factors such as decreased collagen, reduced hydration, and loss of skin elasticity constituting the characteristics of Estrogen Deficient Skin. The presence of estrogen receptors on dermal fibroblasts and epidermal keratinocytes seems to have a direct role in women's skin health. This research examined the efficacy and tolerability of topical Methyl Estradiolpropanoate (MEP) as an anti-aging cosmeceutical with estrogen-like cutaneous effects in an open-label evaluation of postmenopausal women who had never taken hormone replacement therapy (HRT).

The significance of MEP technology is that it is a non-hormonal estrogen receptor activator that specifically addresses signs and symptoms of Estrogen Deficient Skin. Estrogen attenuation begins to take place in perimenopause and is accelerated in menopause. Again, it is important to indicate that MEP is a non-hormonal estrogen receptor activator that is specific to the skin. It is not a hormone, yet, has specific effects on specific skin receptors only. Restoration of estrogen-like skin effects might induce the production of collagen.[5] The ability to stimulate collagen and improve symptoms including dryness, dullness, and fine lines is a benefit to patients with Estrogen Deficient Skin.

In this evaluation, the efficacy of a skin care regimen containing Methyl Estradiolpropanoate for the treatment of facial aging was assessed over 20 weeks. Results showed the regimen improved wrinkles, texture, color, and hydration. Patients in the study indicated very high satisfaction with the formulations of Emepelle Serum and the Night Cream. Younger patients in the study spectrum seemed to show significant improvement by about 8 weeks. Older patients who have been in menopause longer showed notable improvement by 20 weeks.

Further study on the effects of MEP technology may lead to better treatments for premenopausal patients and pre-juvenation skin care regimens.

DISCLOSURE

Joel L. Cohen MD is a consultant for Ferndale Pharma Group, Inc., Ferndale, MI.

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