

## Assessment of Efficacy and Safety of Fixed Dose Combination of 3% Biophytex LS 8740 and 5% Proteasyl TP LS 8657 Cream in the Treatment of Under Eye Dark Circles (Infra-orbital Hyperchromia)

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### Abstract

**Background:** Under Eye Dark Circles is attributed to multiple factors. The treatment should address the various pathologies involved to provide the best possible effects. **Aims:** To assess the efficacy and safety of Wunder eye cream (a combination of 3% *Biophytex LS 8740* and 5% *Proteasyl TP LS 8657*) in patients with under eye dark circles. **Study Design:** Open label, prospective, single arm and multicentric post marketing surveillance clinical study. **Materials and Methods:** 142 patients (125 males and 17 females) were evaluated in the study. Wunder Eye cream was applied twice daily on the affected under eye dark circle area for eight weeks. Parameters evaluated were area of under eye pigmentation, improvement in luminance of under eye skin, reduction in under eye puffiness and reduction in under eye wrinkles using a digital camera photographs after four and eight weeks of treatment. Safety evaluation was also done on the same time. The values were compared using Chi-Square test. **Results:** Early response was seen in 40% of patients with four weeks of treatment where 50% improvement in all the parameters was seen. With eight weeks of therapy about 92.3% of patients showed 50 to 100% improvement in the area of under eye pigmentation; 50% to 75% improvement was seen in 87.3% of patients for under eye pigmentation, in

80.1% patients for luminance of under eye skin, in 68% patients for under eye puffiness and in 67.4% of patients for under eye wrinkles. **Conclusion:** Wunder eye cream is a combination of botanical and yeast extracts was found to be effective against under eye dark circles.

### Keywords

*under eye dark circles, biophytex LS 8740, proteasyl TP LS 8657*

### Key Message

Under eye dark circles result from a variety of reasons including dermal melanin deposition, post inflammatory hyperpigmentation as well as shadowing from lax skin and infraorbital swelling. Its management includes topical treatment (*eg. chemical peels, sunscreens, demelanizing agents, moisturizers, anti-aging lotions and gels*) and surgical treatment (*eg. laser surgery, dermabrasion, face lifts and dermal fillers*). However none of the available topical treatment modalities address all the process for under eye dark circles. There is a need for a therapy which should address the pathological processes involved.

### Introduction

Dark circles under the eyes are defined as bilateral,

round, homogeneous pigment macules on the infraorbital regions<sup>1</sup>. It is an ill-defined entity and a common cosmetic concern popularly known as “infraorbital skin discoloration”, “infraorbital darkening”, “infraorbital hyperchromia”, “darkening of the skin around the eyes” and “periorbital hyperchromic macules and patches”<sup>2,3</sup>. Although dark circle is the most commonly used term for the condition, it is not a formal medical term.

As regard to distribution, the skin below lower eye lid is first involved and with age pigmentation progress to the area of the upper eyelid<sup>4</sup>. The hyperpigmentation may also include the eyebrow, malar bone and half sides of the base of the nose. While there are no statistics giving the frequency of its occurrence, dark circles under the eyelid are definitely a cosmetic concern for a large number of individuals<sup>5</sup>. Dark circles under the eyes are one of the main aesthetic facial concerns that affect individuals of any age, both genders and all races<sup>6</sup>. These dark circles interfere with the face appearance, giving the patient a tired, sad, or hangover look. Disguising the lesions is almost mandatory for some individuals who depend on a well-cared and positive appearance for their work or social activities<sup>7</sup>.

The causes for under eye dark circles include hereditary/genetic factors, stress, allergies and lack of sleep. It has been stated to result from a variety of reasons including dermal melanin deposition, post inflammatory hyperpigmentation from atopic or contact allergic dermatitis as well as shadowing from lax skin and infraorbital swelling<sup>2</sup>. Excessive pseudoherniation of orbital fat is also intimately related to the presence of infraorbital dark circles. Importantly, under eye dark circles is a consequence of poor microcirculation, namely due to increased permeability of the capillaries wherein hemoglobin leaks out and accumulate as hemosiderin in the surrounding tissue. This gives a dark hue to the skin, especially in the under eye area, where the skin is very thin. These visible effects on the skin are sometimes accompanied by skin irritation or a feeling of tension or local warmth, particularly in the case of sensitive skin. There is no doubt that the dark rings are worsened by general fatigue, especially lack of sleep.

While patients in consultation may not mention infraorbital discoloration, many are interested in having it treated once they are informed that it is a treatable condition. Management of under eye dark circles includes topical treatment (eg. *chemical peels, sunscreens, demelanizing*

*agents, moisturizers, anti-aging lotions and gels*) and surgical treatment (eg. *laser surgery, dermabrasion, face lifts and dermal fillers*). However none of the available topical treatment modalities address all the process for under eye dark circles. There is a need for a therapy which should address the pathological processes involved.

Wunder Eye Cream is a combination of 3% Biophytex LS 8740 and 5% Proteasyl TP LS 8657, indicated for the treatment of under eye dark circles. The active ingredient Biophytex LS 8740 is a synergistic vasoactive complex of five botanical and one yeast extract (*Ruscus aculeatus, Centella asiatica, Calendula officinalis, Aesculus hippocastanum, Liquorice and Saccharomyces cerevisiae*), that reinforces capillary tone, increases collagen content and tensile strength of blood vessel wall and thus reduces capillary permeability and leakage and have anti-inflammatory and anti-oxidant effects<sup>8</sup>.

The other ingredient Proteasyl TP LS 8657, is a new botanical anti-protease enzyme complex extracted from seeds of *Pisum sativum L*, and having anti-elastase, anti-collagenase and anti-oxidant properties, and thus protects the degradation of elastin and collagen fibers, causing increased skin firmness and elasticity. It restores the balance between proteases and anti-proteases and also has anti-aging properties. It also produces long lasting moisturization of skin and synthesis of collagen, elastin and glycosaminoglycans leading to skin firmness and improvement in skin elasticity and thus improves the lax skin in patients of under eye dark circles<sup>9</sup>.

A post marketing surveillance study was conducted to further assess efficacy and safety of fixed dose combination of 3% Biophytex LS 8740 and 5% Proteasyl TP LS 8657 cream (Wunder Eye) in the treatment of Under Eye Dark Circles (Infra-orbital hyperchromia).

### **Materials and Methods**

Study was conducted after obtaining Independent Ethics Committee permission. Patients aged between 18-50 years of age, with mild, moderate or severe under eye dark circles and providing written informed consent were enrolled in the study. All topical treatments for under eye dark circles were discontinued two weeks prior to enrollment in study. Patients were excluded if they had a history of hypersensitivity to any ingredients of study drug and if they were pregnant or lactating. Patients on any concomitant

therapy, dermatological disorder or surgical treatment on face that may interfere with the study results were also excluded from the study. Once enrolled, patients were explained procedure to apply Wunder eye cream twice daily in the affected under eye dark circle area for eight weeks.

At the first visit a detailed history was taken, examination was done and a baseline photograph of the affected facial region was taken. During the second visit (end of four weeks) and third visit (end of eight weeks), the assessment for efficacy was done by comparing with the baseline photograph.

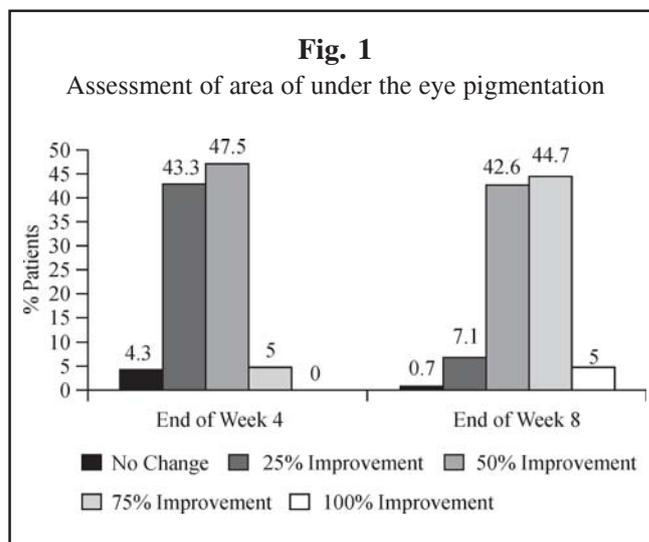
Assessment for efficacy was done based on the following points: area of under eye pigmentation, improvement in luminance of under eye skin, reduction in under eye puffiness and reduction in under eye wrinkles. The following grades were given for comparison: Grade 0: no change; Grade 1: 0-25% improvement; Grade 2: 25-50% improvement; Grade 3: 50-75% improvement; Grade 4: 75-100% improvements. Investigator's and Patient's Global Assessments were done on the second visit (end of 4 weeks) and third visit (end of 8 weeks). All adverse events were noted and evaluated along with the efficacy data. The values were compared for significance using Chi-Square test.

## Results

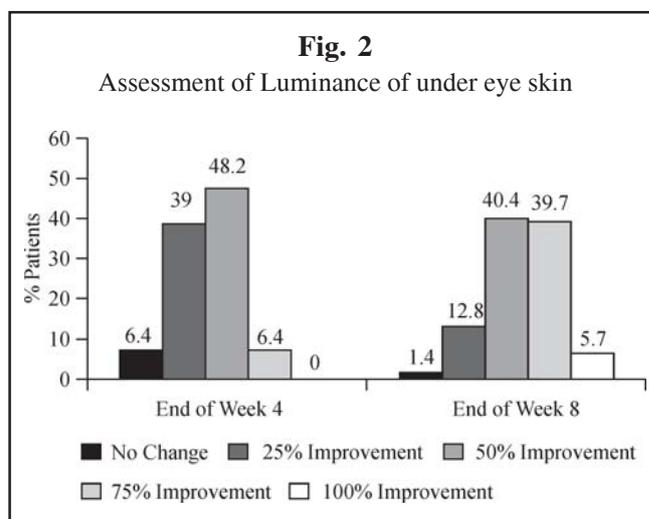
Of the 154 enrolled patients, 142 patients (125 males and 17 females) with a mean age of  $30.4 \pm 7.1$  years were evaluated in the study.

*Assessment of Area of under eye pigmentation at Week four and Week eight:* Overall 92.3% of patients showed 50 to 100% improvement in the area of under eye pigmentation after application of the study drug. 87.3% of patients showed improvement of 50 to 75% whereas 5% of patients showed 100% response in the under eye pigmentation by the end of study. Response rate increased with duration of therapy with significant percentage of patients (44.7%) showing 75% improvement in the under eye pigmentation by week 8 compared to 4 weeks of therapy (5% of patients showing 75% improvement), as shown in **Fig. 1**.

*Assessment of luminance of under eye skin at week four and week eight:* With the improvement in pigmentation, there was a corresponding improvement in the luminance of the under eye skin which was significantly higher at

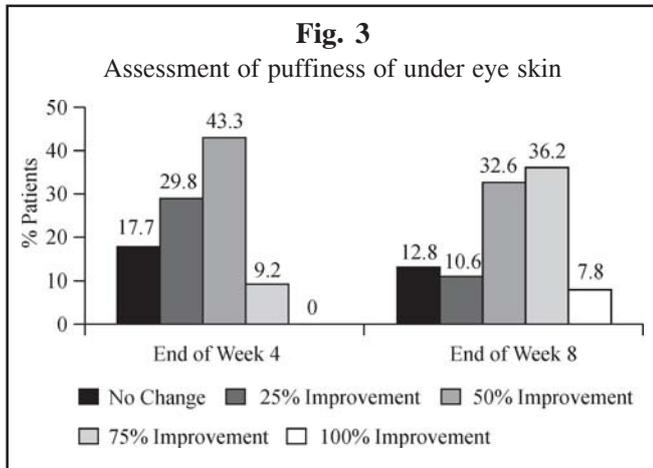


eight weeks of therapy compared to four weeks. By week four, 54.6% of patients showed improvement in the under eye luminance ranging from 50% to 75% which increased to 80.1% by week 8, as shown in **Fig. 2**.

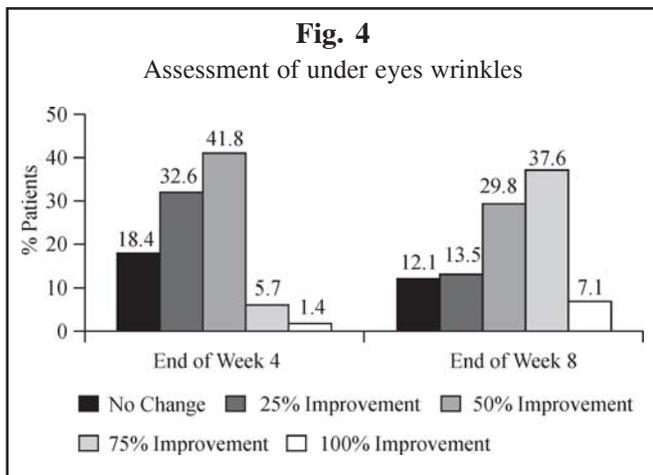


*Assessment Of puffiness of under eye at week four and week eight:* By week four, about 52% of patients showed 50% to 75% improvement in the under eye puffiness and on continuing therapy for eight weeks, a similar improvement was seen in about 68% (**Fig. 3**). 7.8% of patients showed complete resolution of under eye puffiness.

*Assessment Of Under eye wrinkles at week four and week eight:* 50 to 75% reduction in the under eye wrinkles was seen in 67.4% of patients at week eight and 47.5% at week four respectively. Patients who had minimally



responded with four weeks of therapy showed significant improvement on continuing treatment for eight weeks with 37.6% patients showing 75% reduction in under eye wrinkles compared to 5.7% with four weeks therapy. Moreover 7.1% of patients showed complete resolution of under eye wrinkles after eight weeks of therapy as shown in Fig. 4.



*Investigator’s and Patient’s Global Assessment:*

As per the investigator’s assessment, 50% to 75% of improvement was seen in 85.8% and 67.4% of patients with eight weeks and four weeks of therapy respectively. Similarly, improvement of 50% to 75% was seen in 85.1% and 67.4% of patients with eight weeks and four weeks of therapy respectively as per the patient’s global assessment.

The results on week eight were statistically significant compared to week four indicating better results with longer use of the drug.

*Safety Assessment:*

Adverse effects to the therapy was seen in only four patients including local irritation in one patient, burning sensation of eyes in one patient and mild rash in three events. One patient discontinued from the study because of irritation and burning of eyes.

**Discussion**

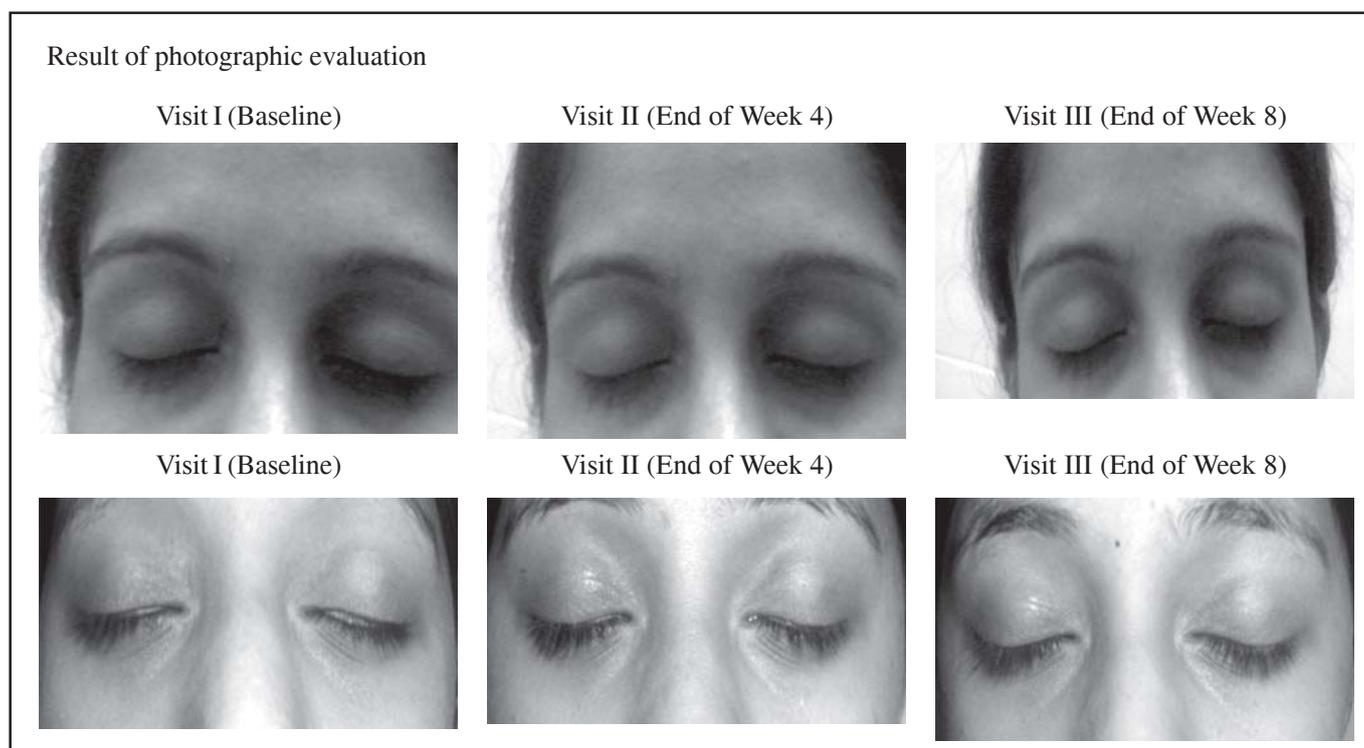
Infraorbital dark circles affect both males and females, with a wide range of age and the conditions is known to worsens with the advancing age<sup>10</sup>. Although it does not cause morbidity, it can influence the quality of life. It is a significant cosmetic concern especially for female patients and is gaining increased attention in recent times<sup>10</sup>.

Despite its significant prevalence, there are only few published studies about its exact pathogenesis. Dark circles under the eyes are attributed to multiple etiologic factors that include melanin deposition, post inflammatory hyperpigmentation, skin laxity and others. The pigmentation looks darker when they are present below bulging lower eyelids which add a shadow effect and worsen the appearance<sup>10</sup>.

Various treatment modalities are available including invasive and non-invasive, pharmacological and non-pharmacological, however none without their side effects<sup>5</sup> or able to address all the above processes contributing to under eye dark circles with many taking a long time for complete recovery.

Wunder eye cream is a combination of botanical and yeast extracts with their protective mechanisms against the pathology responsible for under eye dark circles. It is composed of Biophytex LS 8740 3% and Proteasyl LS 8657 5% which is a synergistic complex of 6 botanical and yeast extracts which compliments each other’s action. The active ingredients of Wunder Eye Cream bring about a combination of beneficial effects including decreased capillary permeability, anti-inflammatory and anti-oxidant effects, anti-aging effect, moisturization of skin and increased collagen synthesis with increased skin firmness and elasticity, all beneficial in the treatment of under eye dark circles.

Wunder Eye cream had undergone post marketing clinical trial to allow detailed analysis of its efficacy and safety. The above study gives the results of 142 patients with mild to severe under eye dark circles. The study



addresses the related cosmetic problems including pigmentation, luminance, under eye puffiness and wrinkles and treatment with Wunder Eye cream.

The results showed that about 45% improvement in the above parameters was seen in a large number of patients within the first 4 weeks of application of Wunder Eye cream.

With 8 weeks of treatment with Wunder Eye cream, 50 to 75% improvement in the under eye pigmentation and under eye luminance was seen in about 80% of patients. These results appear to be better than many other treatments mentioned in the literature.

Traditionally, depigmenting agents have been used for the reduction of the pigmentation. Hydroquinone is the most prescribed bleaching agent world-wide and is still the criterion standard for the treatment of hyperpigmentation. Though Hydroquinone shows acceptable beneficial effects, it is recommended that depigmenting agents has to be continued for several months before cosmetic benefits are obtained<sup>10</sup>. In an early study assessing the clinical efficacy of hydroquinone, the depigmenting effects become evident after five to seven weeks, usually preceded by erythema and scaling. Treatment was continued for at least three months and up to one year<sup>10</sup>.

As compared to the above, treatment with Wunder Eye cream resulted in more patients showing improvement in eye pigmentation and with lesser duration of therapy. Moreover, under eye puffiness and under eye wrinkles were reduced by 50% to 75% in about 65% of patients which can be considered to be better as compared to the above examples. In fact the beneficial role in effectively reducing under eye wrinkles is an encouraging sign for further evaluation.

In this study, only four patients complained of adverse events and only one patient withdraw from the study. Wunder Eye cream appears to be a safer alternative in the management of hyperpigmentation. Also we need to remember that any treatment designed to reduce hyperpigmentation will be most effective when used in conjunction with steps taken to reduce exposure to factors that contribute to hyperpigmentation.

### Conclusion

Since various factors are operating to cause infraorbital dark circles, for the therapy to be effective it should have actions on most of the pathologies. Wunder Eye Cream is a combination product with additive effects suitable for the treatment of under eye dark circle and other cosmetic

problems including under eye wrinkles as seen in this study. Wunder Eye Cream bring about an early beneficial effects in a larger number of patients with lesser incidence of adverse effects. The above results encourage the use of Wunder Eye Cream as an effective eye-care cosmetic product with the purpose of reducing under eye dark circles of any severity.

#### Key Message

Wunder eye cream is a combination of botanical and yeast extracts with their protective mechanisms against the pathology responsible for under eye dark circles. It is composed of Biophytex LS 8740 3% and Proteasyl LS 8657 5% which is a synergistic complex of 6 botanical and yeast extracts which compliments each other's action. The active ingredients of Wunder Eye Cream bring about a combination of beneficial effects including decreased capillary permeability, anti-inflammatory and anti-oxidant effects, anti-aging effect, moisturization of skin and increased collagen synthesis with increased skin firmness and elasticity, all beneficial in the treatment of under eye dark circles.

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