

EDONELLE - EDONELLE INTENSE

**TECHNICAL AND SCIENTIFIC
DOSSIER**

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CHAPTER I Introduction

The urogenital tract, specifically the vagina, urethra, bladder, trigone of the bladder, and pelvic floor muscles, contains estrogen receptors. Estrogen is needed for the health of these tissues and structures, a lack of which causes them to undergo atrophy (Castelo-Branco and Rostro, 2007; Nappi and Kokot-Kierepa, 2012).

During the menopause transition and postmenopausal periods, women can experience a number of symptoms primarily due to estrogen depletion that include vasomotor and urogenital symptoms.

Vasomotor symptoms include hot flashes, night sweats, insomnia, and mood swings, whereas urogenital symptoms include vaginal dryness, itching, discharge, dysuria (i.e., pain while urinating), and dyspareunia (i.e., pain during sexual intercourse) (Haines et al., 2005; Nappi and Kokot-Kierepa, 2012; Pastore et al., 2004; Willhite and O'Connell, 2001).

Although vasomotor symptoms typically resolve over time, urogenital symptoms remain a persistent consequence of estrogen depletion (Winneker and Harris, 2011).

Postmenopausal vaginal atrophy (PVA) is the term used to describe the group of urogenital symptoms that arise due to estrogen depletion and is also known as urogenital atrophy, vulvovaginal atrophy, and atrophic vaginitis (Mac Bride et al., 2010; Willhite and O'Connell, 2001).

Approximately 10%–50% of postmenopausal women experience symptoms of vaginal atrophy, but only about 25% of them seek medical treatment (NAMS, 2007; Nappi and Kokot-Kierepa, 2012).

It is estimated that in Italy about 7 million women are affected by AVV; more than 50 million women in the European Union.

The recent EU REVIVE study, conducted in 4 European countries including Italy, on 1,000 Italian post-menopausal women (aged 45-75 years) with at least one symptom of AVV, showed that the most frequent symptom is vaginal dryness (78%) combined with pain during sexual activity, considered the most unpleasant symptom (76%).

Women said that symptoms of AVV have a significant impact on their intimate life (69%) and ability to have pleasant sexual intercourse (74%), as well as their feeling of sexual spontaneity (70%).

EU REVIVE showed that 75% of Italian post-menopausal women with AVV interviewed are sexually active, but their sexual stimulus and sexual desire is significantly reduced as a possible consequence of AVV symptoms.

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CHAPTER II Technical Product Sheet

EDONELLE INTENSE PRODUCT

EDONELLE INTENSE is an oleogel topical vaginal formulation (based on CBD, COLEUS BARBATUS, VISNADINE ad TERPENS): to improve symptoms related to vulvovaginal atrophy (AVV), including vaginal dryness and the consequent dyspareunia (pain during sexual intercourse).

EDONELLE INTENSE produces effect increasing blood circulation in glans, clitoris and labia majora increasing sensitivity and reactivity. It helps natural production of vaginal secretions, making the intercourse easier and pleasing.

CBD interacts with several receptors on peripheral organs, dilating blood vessels and stimulating the release of dopamine, the neurotransmitter at the base of the mechanism of sexual excitation.

Visnadine increases regional vascularization, turgidity, sensorial threshold, vasodilatory action favouring the attraction of blood on the clitoris and small lips, increasing excitement and sexual response.

*Coleus Barbatu*s used topically stimulates microcirculation, promotes lubrication and supports orgasm.

INCI

Cbd 1%, Visnadina 1%, Coleus barbatu 1%, Alchool 95%, Wheat germ oil, Micronized silica, MCT triglycerides oil, Sweet almond oil

HOW TO USE

Apply 3/4 delivered doses (1,5-2 ml) directly on vulvar or clitoris area some minutes before intercourse.

CERTIFICATION AND INFO

- DERMATOLOGICALLY TESTED
- GINECOLOGICALLY TESTED
- HEAVY METALS TESTED
- MICROBIOLOGIC CHALLENGE
- PARABEN-FREE

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- 15 ml – PAO 12M

CHAPTER III Active ingredients

EDONELLE INTENSE contains the following active ingredients:

- CANNABIDOL
- VISNADINE
- COLEUS BARBATUS
- TERPENS

The effectiveness of the product is the result of the synergy of CBD with other 2 phytotherapeutic active ingredients that guarantees an increase of:

- A. VAGINAL MICROCIRCULATION
- B. TURGIDITY OF THE CLITORIS
- C. INTENSITY OF ORGASM
- D. LUBRICATION
- E. MYORELAXANT ACTION
- F. PAIN RELIEF

CANNABIDOL

Cannabis is a plant that contains within it a large group of pharmacologically active chemical compounds, the most important from a pharmaceutical point of view are cannabinoids.

Of all cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD) are the best known: it was found that these compounds have very different pharmacological activity despite having similar chemical characteristics.

THC is in fact the most important cannabinoid with psychoactive effect while CBD is the main cannabinoid without this effect.

Regarding the mechanism of action cannabinoids mimic the behaviour of other molecules that our body naturally produces: endocannabinoids.

Studies have shown that endocannabinoids play an important role in maintaining the right balance in the body.

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In particular, in case of illness, the endocannabinoid system helps the body to feel less pain, control spasms, relax, deal with post-traumatic stress, regulate sleep-wake rhythms and safeguard the nervous system.

Therefore CBD interacts with many receptors both at central and peripheral organ level with multiple effects and relapses also in the sexual sphere.

In particular, it has been seen that CBD has effects on sexual desire, because when given locally:

- “Promoting blood flow and lubrication”: For those who struggle with dryness and painful sex, adding a lubricant can improve sexual performance and relieve pain. Many CBD manufacturers are making lubricants that incorporate CBD as a means to enhance sexual pleasure. Researchers have studied the effects of topical CBD as a dermatology treatment. According to several studies, topical CBD has an anti-inflammatory effect, which could theoretically make sex more comfortable. However, there aren’t any studies specific on CBD and lubrication”. “Topical, whole plant CBD balm can help women experiencing painful sexual intercourse due to vaginal dryness or to irritation at the vaginal opening to have more comfortable and enjoyable sexual experiences,”
- “Dilates blood vessels”: “CBD increases blood flow and nerve sensation, which can help enhance sexual pleasure and intensify orgasms”
- “Effects on pain”: Cannabidiol is an effective anti-inflammatory. In addition, local use with a balm or oil can help the woman stimulate natural vaginal lubrication by reducing pain caused by dryness or irritation.

VISNADINE

Visnadine is an active ingredient of the fruit of Ammi Visnaga, a plant belonging to the Umbelliferae family, traditionally used in cardiovascular disorders and in particular in the treatment of angina pectoris and various peripheral vascular diseases, plant widely used in Egyptian medicine since the Pharaohs times.

Female sexual dysfunction (FSD) is a generic term that refers to difficulties that occur during the sexual response cycle and that impede the woman pleasure during sexual activity.

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The growing interest in the improvement of women's sexual function provided by the topical vaginal application of Visnadina (a natural extractive substance with vasodilatory properties) has been evaluated in high number of recent clinical trials.

Blind vs. placebo clinical study by Sparavigna A., et al. (2019), evaluated the vessel kinetic activity of a Visnadine gel on the genital mucosa membrane of 15 healthy postmenopausal women investigating the effectiveness of the treatment according to the subjective judgment of women by measuring the heat, degree of lubrication and sensations at the vaginal level. This research has shown that a single application of Visnadine resulted in a significant increase in vaginal hyperemia, accompanied by a significant increase in local turgor compared to placebo. The women reported a pleasant feeling of well-being.

Topical use of Visnadine: •increases regional vascularization

- increases turgidity and sensorial threshold
- increases vasodilatory action favouring the attraction of blood on the clitoris and small lips
- increasing excitement and sexual response

COLEUS

Forskolin is a chemical found in the roots of the plant *Plectranthus barbatus* (Coleus forskohlii).

Medical researchers have documented that Coleus roots contains a potent compound called Forskolin that may have muscle relaxant properties and can dilate blood vessels. The forskolin has been found to regulate various enzymes and hormones in human body.

Forskolin is used for the treatment of allergies, respiratory problems, cardiovascular diseases, glaucoma, psoriasis, hypothyroidism, weight loss,eczema, asthma, psoriasis and hypertension. Recently, it was reported as a natural remedy for urinary tract infections (UTI) by enhancing the ability of antibiotics to kill the bacteria that cause 90 % of infections in the bladder. (Rupp et al., 1986).

Topical use of Coleus Barbatus:

- stimulating microcirculation
- promoting lubrication
- promoting orgasm

CHAPETR IV Pilot Clinical Study

Efficacy and safety of 2 topical vaginal oleogel formulations* (Oleogel A and Oleogel Intense): analysis of 110 women.

SUMMARY

Many women have problems with sex a different stage in their life and according to data, Female sexual Dysfunction (FSD) affect around 1- 3 young and middle-aged women and around 1 in 2 older women. The reason behind sexual dysfunction are both physical and psychological factors and different symptoms (less desire for sex, not being able to have an orgasm, having pain during sex, etc.). There are some natural active ingredients (included CBD) can help to overcome and resolve these problems. We aimed to assess the safety and efficacy of 2 topical oleogel vaginal formulation containing CBD and other natural ingredients (Visnadine, Coleus Barbatius and terpenes.).

METHODS

We conducted a pilot test involving 110 women:

- a. 50 women of age 18-45, where we tested a formulation with CBD, Visnadine and terpenes (*Oleogel A*)
- b. 60 women of age 46 – 65 were we tested a formulation with CBD, Visnadine, Coleus Barbatius and terpenes (*Oleogel Intense*)

After twice use per participant, we assessed the efficacy (4 KPIs) and the safety (2 KPIs) through a questionnaire.

Products: we tested 2 formulations (patent pending): I. *Oleogel A* (oleogel with CBD, terpenes and Visnadine oil) and *Oleogel Intense* (oleogel with CBD, terpenes, Visnadine + Coleus oil mix).

FINDINGS

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I. Oleogel A results

After twice use of *Oleogel A* at the dosage of 1-1,5 ml (2-3 delivered dose), 42 women out of 50 affirmed to have increased significantly the pleasure during sex.

With high score on: I. More intense orgasm (3.9), II. Warmth sensation (3.8), III. Lubrication increase (4.3).

High safety perception (skin burning and/or skin rash feeling) has been reported with an average score of 4.3 - see *table I.a*

II. Oleogel Intense results

Oleogel Intense has been used at dosage of 1,5-2 ml range (3-4 delivered dose); 50 women out of 60 reported high score (>4 point out of 5) on more intense orgasm (4.3) and Increase lubrication (4.7).

This formulation confirmed an high safety perception on skin burning and/or skin rash feeling - see *table I.a*

Table I.a

Efficacy and Safety

Parameters	Oleogel A - women % (n)		Oleogel Intense - women % (n)	
	Yes*	No*	Yes*	No*
Efficacy (Yes / No)	84% (42)	10% (5)	89% (53)	7% (4)
• More intense orgasm (score 0 - 5)**	3.9		4.3	
• Multiple orgasms (score 0 - 5)**	3.0		2.8	
• Warmth sensation (score 0 - 5)**	3.8		3.1	
• Increase lubrication (score 0 - 5)**	4.3		4.7	
Safety Perception (score 0 - 5)**	4.3		4.6	

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Note

* Efficacy: 6% undecided Oleogel A
4% undecided Oleogel Intense

** Score: 0 poor - 5 excellent

CHAPTER V Intellectual Property

PARTNER: Barzanò & Zanardo
more than twenty years experience in pharma

PHASE: Italian patent application (May 2020)

NEXT: PCT procedure by the end of 2020

PATENT STRATEGY: synergistic action of CBD and terpenes (as a homogeneous class of extracts)

A generic "entourage" effect is referred in the literature:

Our focus on synergistic data in a cell model related to anti inflammatory activity

CHAPTER VI SITOGRAFI

GENERAL

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COLEUS

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Blind_Parallel_Design_Trial_of_the_Efficacy_and_Safety_of_ZestraR_in_Women_With_Mixed_DesireInterestArousalOrgasm_Disorders

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VISNADINE

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