Neo migraine prevention - a dietary supplement for migraine prevention with its own scientific study, in the form of orally dispersible tablets

Product Advantages

- Neo migraine prevention is an effective dietary supplement with its own scientific study, contributing to long-term prevention of migraine attacks, and containing a unique combination of natural active ingredients.
- The product is developed in a cooperation with First Faculty of Medicine, Charles University and its workplace, Biotechnology and Biomedicine Center of the Academy of Sciences and Charles University in Vestec (Biocev).
- It´s the only product on market with scientifically proven high cell absorption and solubility of active ingredients - extracts of Tanacetum parthenium (Feverfew) and Scutellaria baicalensis (Baical skullcap).
- User-Friendly form - tablets dissolve quickly in the mouth (ODT), water no needed
- A unique and innovative solution – tablets release the contained active ingredients directly through the mucous membrane of the oral cavity. Thanks to the advanced formulation approach, the active substances are released and absorbed in the oral cavity and the upper part of the esophagus, thus avoiding the passage of the liver. **This results in much higher efficiency even at low doses.** If the active ingredients were administered in a classic tablet, majority of administered dose would be destroyed or converted into ineffective substances through the passage the digestive tract and the liver, thereby **reducing the effectiveness of the administered dose.**
- The tablet **rapidly** (within 40 seconds) releases the **main active ingredients of the standardized extract of Feverfew** (up to 60% of parthenolides) and Skullcap (up to 85% of baicalin).
- These extracts and their active substances are formulated to penetrate faster into the human body cells. **Parthenolides released from Neo migraine prevention are absorbed through the cell membrane model 300 times more than competing products. Baicaline in up to 1,5 times more than competing products**
- The product contains **L-theanin and vitamins B1 and B6** to promote the effects of the extracts of the Feverfew and Skullcap. L-theanin helps the release and prevention of anxiety attacks, Complex of vitamins B contributes to good condition of nervous system.

Product description

- **Neo migraine prevention** contains only substances of natural origin
- **User friendly form** - tablets (8 mm in diameter) dissolve in mouth to 40 seconds without needed a water
- Recommended usage – 2 tablets daily
- Available for vegans and vegetarians

Scientific Study (20.5.2018)

In the context of research and development cooperation between mcePharma s.r.o. and First Faculty of Medicine, Charles University and its workplace Biotechnology and Biomedicine Center of the Academy of Sciences and Charles University in Vestec (Biocev), increased solubility and cell absorption of the Feverfew and Skullcap extracts active substances was achieved, in order to incorporate extracts in orally dispersible tablets (ODT) for effective prevention of migraine attacks.

Neo migraine prevention contains an extract of Feverfew, a herb traditionally used for the prevention of migraine and headaches in general. Main active substances are parthenolides. Contemporary scientific research of parthenolides is focused on their anti-inflammatory activity[1,2] and effects on smooth muscle vasculature[3,4]. It is believed that these effects cause high efficacy in the prevention of migraine attacks and headaches.

For Baical skullcap, numerous scientific studies have shown a strong effect against migraine attacks in rats (*in vivo*), to which the migraine was artificially induced.[5] Another benefit is the efficacy of Baical skullcap for pain relief.[6]

To support the effect of both extracts, supportive active ingredients were added to the formulation, which preventively contributed to good nervous system conditioning and psychological relaxation (Table 1)

Table 1: Active ingredients of Neo migraine prevention dietary supplement

Active ingredient		Tablet content (mg)	Effects
Feverfew extract (0,8 % Parthenolides)		5.0	Pain relief (migraine, headache), Convulsions relief, fever
Baical skullcap extract (85 % baicalin)		5.0	Increases stress resistance, convulsion relief
L-theanine		1.0	Anxiety relief and prevention
B-Complex	**Vitamin B1**	0.3	Contributes to better condition of nervous system
	Vitamin B6	0.4	

One of the problem associated with administration of the feverfew extract is the lack of solubility of the active substances - parthenolides. It is possible to increase solubility the formation of complexes with a suitable substance. The formation of these complexes is governed by stoichiometric ratios of the active substances, in the case of parthenolides and complexing compounds. Upon subsequent contact with the body fluids, the parthenolides are released from these complexes. In the pharmaceutical industry, inclusion complexes and chelates are widely used. This procedure can also be used to adjust the solubility of parthenolides.

To ensure the maximum effect of the Feverfew extract and the parthenolides that are poorly soluble in water, a sophisticated procedure has been used to increase the solubility of said substances by 100%. This was achieved by the formation of an inclusion complex containing parthenolides already in the

solid state. By combining the ODT dosage form, the increased solubility of the parthenolides and their accelerated release in oral cavity was achieved, where parthenolides are also absorbed. Main aim of experiments was to prove accelerated release of parthenolides and baicalin through the model of cell membrane in comparison to competitive products A, B (containing Feverfew extract) and competitive products C, D (containing Baical skullcap).

The following parameters were studied in the study:

1. Increased absorption through model membrane

Procedure: The aim of this experiment was to compare absorption of active ingredients (parthenolides nad baicalin) released from Neo migraine prevention tablet and competetive products, through the model of cell membrane. In experiment, model membrane (ROTH, MembraCel™) was used. For analytics, LC-MS spectrophotometry was utilized.

Results: Parthenolides released from Neo migraine prevention tablet in high amount pass through the model membrane. In comparison to competetive products A and B, up to 300 times more parthenolides pass through model membrane. (Figure 1)

Baicalin released from Neo migraine prevention tablet in high amount pass through the model membrane. In comparison to competetive products C and D, up to 1.5 times higher baicalin amount pass through model membrane. (Figure 2)

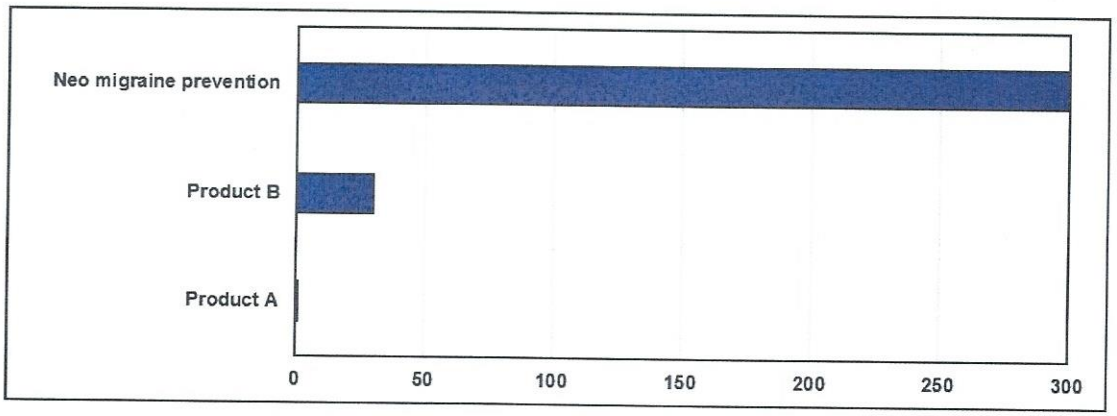

Figure 1: *Absorption of parthenolides through the model membrane. In comparison to competetive products A and B, up to 300 times more parthenolides pass through model membrane*

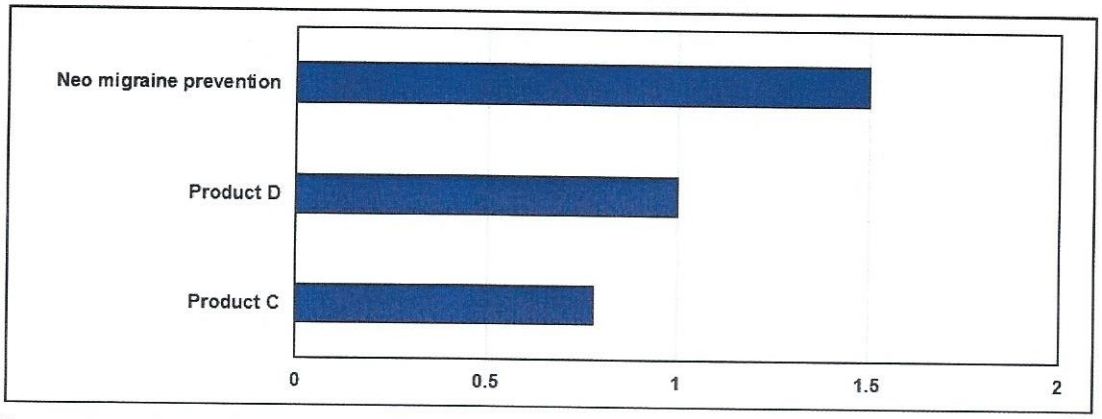

Figure 2: *Absorption of baicalin through the model membrane. In comparison to competetive products C and D, up to 1.5 times higher baicalin amount pass through model membrane*

2. Comparison of the release rate of active substances – parthenolides and Baicalin

Procedure: The aim of this experiment was to compare the release rate of parthenolides from Neo migraine prevention tablets and two competitive products and containing the extracts by HPLC-MS (High Performance Liquid Chromatography by Simultaneous Evaluation by Mass Spectrometry) The release of baicalin was also evaluated with same method.

Results: For Neo migraine prevention, 60% of parthenolides is released within 40 seconds after administration, meanwhile only 10% of this active substance is released in commercially available products. (Figure 3)

In the case of baicalin, up to 85% of the content is released within 40 seconds of tablet after administration, meanwhile only 40% of the active substance is released in commercially available products. (Figure 4)

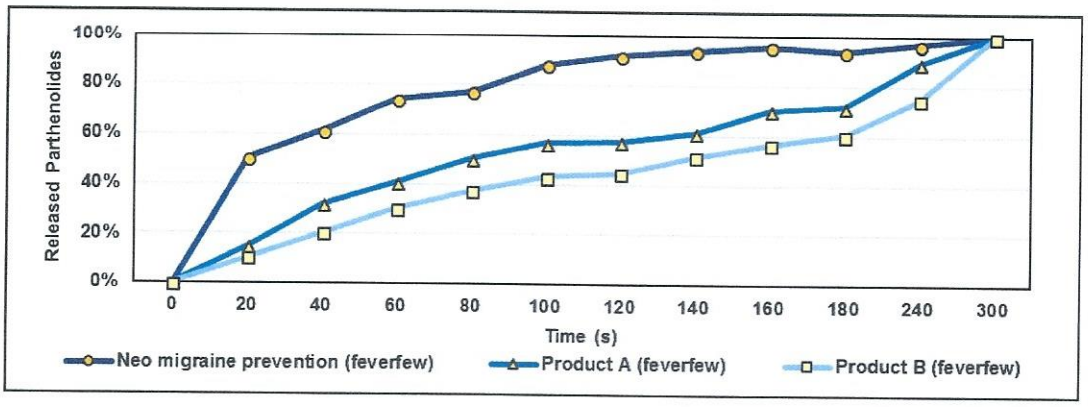

Figure 3: *Relative percentage of parthenolide release rate into the solution. For Neo migraine prevention, 60% of parthenolides is released within 40 seconds after administration.*

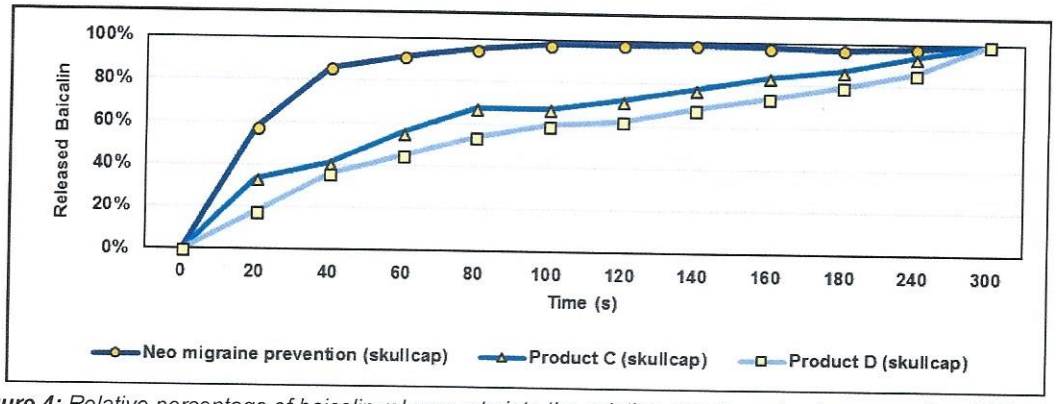

Figure 4: *Relative percentage of baicalin release rate into the solution. For Neo migraine prevention, 85% of baicalin is released within 40 seconds after administration.*

Conclusion:

- Neo migraine prevention is an effective dietary supplement with its own scientific study, contributing to long-term prevention of migraine attacks, and containing a unique combination of natural active substances.
- The product is developed in a cooperation with First Faculty of Medicine, Charles University and its workplace Biotechnology and Biomedicine Center of the Academy of Sciences and Charles University in Vestec (Biocev).
- It´s the only product on market with scientifically proven high cell absorption and solubility of active ingredients - extracts of Feverfew and Baical skullcap.
- User-Friendly form - tablets dissolve quickly in the mouth (ODT), water no needed
- A unique solution – tablets release the contained active ingredients directly through the mucous membrane of the oral cavity. Thanks to the advanced formulation approach, the active substances are released and absorbed in the oral cavity and the upper part of the esophagus, thus avoiding the passage of the liver. This results in much **higher efficiency even at low doses**. If the active ingredients were administered in a classic tablet, majority of administered dose would be destroyed or converted into ineffective substances through the passage the digestive tract and the liver, **thereby reducing the effectiveness of the administered dose**.
- The **tablet rapidly** (within 40 seconds) **releases the main active ingredients of the standardized extract of Feverfew** (up to 60% of parthenolides) and **Skullcap** (up to 85% of baicalin).
- These active substances are formulated to penetrate faster into the human body cells. **Parthenolides released from Neo migraine prevention are absorbed through the cell membrane model 300x times more than competing products. Baikaline in up to 1,5x times more than competing products**
- The product contains **L-theanin and vitamins B1 and B6** to promote the effects of the extracts of the Feverfew and Skullcap. L-theanin helps the release and prevention of anxiety attacks, Complex of vitamins B contributes to good condition of nervous system.

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mcePharma s.r.o.

Budovatelska 1178/35

743 01 Bilovec

Czech Republic

Represented by:

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Ing. Ivan Mikeš, CSc.
(Managing director)

www.mcepharma.com
Contact: sales@mcepharma.com

BIOCEV, First Faculty of Medicine, Charles University

Katerinska 1660/32,

Praha 2, 121 08

Czech Republic

Represented by:

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Professor Vladimír Král, Ph.D., DSc
(Project director)

Univerzita Karlova
1. lékařská fakulta - Ústav BIOCEV
Průmyslová 595, 252 50 Vestec
IČ: 00216208 DIČ: CZ00216208

References:

1. Kwok B., H. et al.: The anti-inflammatory natural product parthenolide from the medicinal herb feverfew directly binds to and inhibits IkappaB kinase. Chem. Biol., 8, 2001, 759–766.

2. Neill L., A. et al.: Extracts of feverfew inhibit mitogen-induced human peripheral blood mononuclear cell proliferation and cytokine mediated responses: A cytotoxic effect. Br. J. Clin. Pharmacol.,23, 1987, 81–83.

3. Bejar E. et al.: Parthenolide inhibits the contractile responses of rat stomach fundus to fenfluramine and dextroamphetamine but not serotonin. J. Ethnopharmacol., 50, 1996, 1–12.

4. Vibhavari S. et al.: Annual Reports in Medicinal Chemistry: Recent Recent Developments in Targeting Neuroinflammation in Disease, 2012, 37 – 53.

5. Sun Y., Y. et al.: Baicalin Alleviates Nitroglycerin-induced Migraine in Rats via the Trigeminovascular Systém. Phytother. Res., 31 (6), 2017, 899-905.

6. Song, C., H., et al.: Effects of Theanine on the Release of Brain Alpha Wave in Adult Males. Korean J. Nutr. 36, (9), 2003, 918-923.

7. Ritsner, M. S., et al.: L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study. J. Clin. Psychiatry., 72, (1), 2011, 34-42.