



Incoxil

patented dietary supplement for
stronger pelvic floor muscles
and less urinary incontinence

At a Glance



Unmet need

25 to 57% of all women in the U.S. experience urinary incontinence (UI). In the USA UI is a significant economic burden, with annual cost estimates ranging from \$19.5 billion to more than \$76 billion with growing tendency.



Market

Revenue in the incontinence treatment drug segment amounts to US\$4.18bn in 2020. The market is expected to grow annually by 3.8% (CAGR 2020-2027). Currently no preventative measure, nor treatment is known to targeting the pelvic floor muscle strength without side effects.



Safety and efficacy

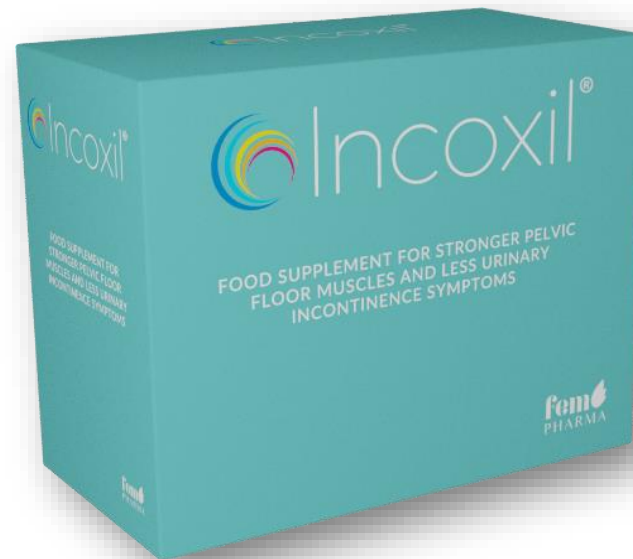
No side effects were reported. Significantly greater strengthening in vaginal squeeze pressure, greater improvement in the Biomechanical Integrity Score and larger decrease in PGI-S score compared to control. Women in the treatment group on average improved twice as much in their BI-score as women in the control group.



Solution

Pelvic floor muscle training (PFMT) is globally recommended as part of first-line treatment and is proven to work for all women with stress or mixed urinary incontinence.

In order to increase the effectiveness of PFMT, we have developed a special dietary supplement INCOXIL with active ingredients of Creatine, Leucine, Calcium, Magnesium, and Zinc



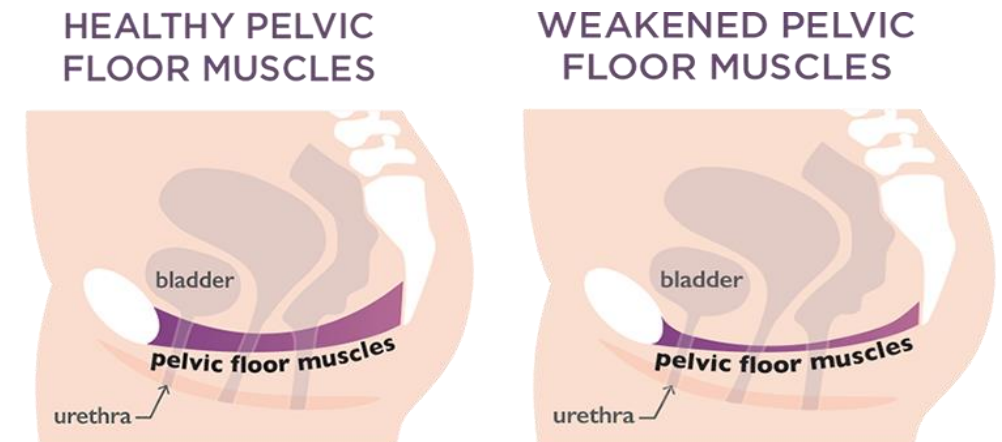
IP protection

US Patent Application was submitted "Pharmaceutical Composition and Method for Improving Biomechanical Integrity of the Pelvic Floor"

APPLICATION NUMBER:
63438705

Unmet need

- 25 to 57% of women in the U.S. experience urinary incontinence (UI).
- UI is a significant economic burden, with annual cost estimates ranging from \$19.5 billion to more than \$76 billion with growing tendency in the U.S.
- Women with UI are at a 30% greater risk of hospitalization and twice as likely to be admitted to a nursing facility.
- During pregnancy, urinary incontinence is also a common phenomenon affecting between 30 and 60% of all pregnant women and which regresses in more than half of the women after delivery.
- No proven pharmaceutical treatment is currently available for stress dominant UI.



Incontinence Drug Market

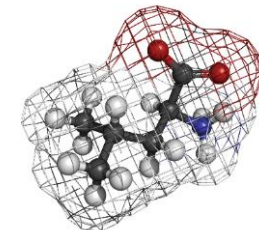
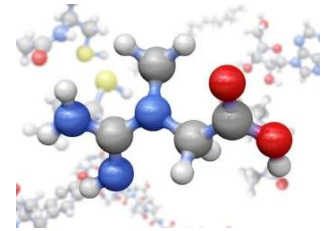
- Revenue in the incontinence treatment drug segment amounts to US\$4.18bn in 2020. The market is expected to grow annually by 3.8% (CAGR 2020-2027).
- Increasing number of regulatory approval for drugs is driving growth of the global urinary incontinence treatment drugs market. Many companies offer drugs in the USA such as Johnson & Johnson, Pfizer, Astellas Pharma, Allergan, Takeda, Merck and Sanofi.
- Currently marketed drugs are anticholinergics/anticonvulsants, skeletal muscle relaxants, antidepressants, alpha blockers, topical estrogens which have low efficacy and/or have unfavorable side effects.
- Currently there is no treatment available on the market targeting the pelvic floor muscle strength without side effects.

Psychological Elements

- 🌿 Urinary incontinence in women is a common problem. The most common form is stress incontinence (50%), followed by mixed stress-urge incontinence (40%). Incontinence is often difficult to treat.
- 🌿 Incontinence causes a major reduction in the quality of life for women of all age groups.
- 🌿 Every form of incontinence has psychological consequences: shame and insecurity are often results of uncontrolled loss of urine. Among others, in the long term, they lead to the avoidance of social contacts and possibly to depression and isolation.
- 🌿 As few as 25-30% of women with UI seek treatment from their healthcare professional.
- 🌿 Awareness that such symptoms can be treated by pelvic floor muscle training and supporting dietary supplementation.
- 🌿 Once she is aware of that, she will know that there is a very good solution that can assist her: INCOXIL.

Solution

- 🌿 Pelvic floor muscle training (PFMT) is globally recommended as part of first-line treatment and is proven to work for all women with stress or mixed urinary incontinence. In order to increase the effectiveness of PFMT, we have developed a special dietary supplement.
- 🌿 CREATINE is an amino acid located mostly in the human body's muscles where it's used for energy. Oral creatine use allow to do more work, leading to greater gains in strength, muscle mass and performance.
- 🌿 ZINC is the second most common trace mineral in the human body. Zinc is involved in a large variety of metabolic processes, accelerates the regeneration of connective tissues and the healing of wounds.
- 🌿 CALCIUM and MAGNESIUM contributes to normal muscle function. Magnesium contributes to a reduction of tiredness and fatigue. Calcium contributes to normal neurotransmission
- 🌿 LEUCINE is an essential amino acid (cannot be made by the body, it must come from food). Leucine is the only nutritional amino acid capable of stimulating the synthesis of muscle proteins. It enhances regeneration and prevents muscle tissue from degradation.



Mechanism of Action: Creatine

- ☞ Creatine is the primary constituent of phosphocreatine, which is used to regenerate ATP within the cell. The human body needs to replenish about 1–3 g of creatine per day to maintain normal creatine stores depending on muscle mass.¹⁻³ (13-15) About half of the daily need for creatine is obtained from the diet.^{4,5}
- ☞ The European Food Safety Authority (EFSA) has approved several health claims for creatine, including that daily creatine consumption can enhance the effect of resistance training on muscle strength in adults over the age of 55 and that creatine increases physical performance in successive bursts of short-term, high-intensity exercise.⁶
- ☞ Creatine supplementation increases intramuscular creatine concentrations, which may help explain the observed improvements in high-intensity exercise performance.⁵
- ☞ Evidence supports that creatine supplementation may improve health status as individuals age and increase strength and/or muscle mass.⁷
- ☞ Previous studies have shown that even long-term supplementation with creatine (up to 30 g/day for five years) is safe and well-tolerated in healthy individuals and the elderly as well.⁵
- ☞ Increased vaginal-pelvic muscle strength and activity may result in better urinary function, especially in women with SUI. Since pelvic floor muscle exercise has been shown to improve the symptoms of stress incontinence, and creatine supplementation may augment muscle training. We believe that women with stress urinary incontinence might benefit from supplementation with creatine while practicing pelvic floor muscle exercises.

1 Harris RC, Soderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. *Clin Sci (Lond)* 1992 Sep;83(3):367-374.

2 Hultman E, Soderlund K, Timmons JA, Cederblad G, Greenhaff PL. Muscle creatine loading in men. *J Appl Physiol* (1985) 1996 Jul;81(1):232-237.

3 Balsom PD, Soderlund K, Ekblom B. Creatine in humans with special reference to creatine supplementation. *Sports Med* 1994 Oct;18(4):268-280.





4 Brosnan ME, Brosnan JT. The role of dietary creatine. *Amino Acids* 2016 Aug;48(8):1785-1791.

5 Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, et al. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. *J Int Soc Sports Nutr* 2017 Jun 13;14:18-017-0173-z. eCollection 2017.

6 EFSA Panel on Dietetic Products, Nutrition and Allergies,(NDA). Scientific Opinion on the substantiation of health claims related to creatine and increase in physical performance during short-term, high intensity, repeated exercise bouts (ID 739, 1520, 1521, 1522, 1523, 1525, 1526, 1531, 1532, 1533, 1534, 1922, 1923, 1924), increase in endurance capacity (ID 1527, 1535), and increase in endurance performance (ID 1521, 1963) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA Journal* 2011 07/01; 2022/10;9(7):2303.

7 Candow DG, Chilibeck PD, Forbes SC. Creatine supplementation and aging musculoskeletal health. *Endocrine* 2014 Apr;45(3):354-361.

Mechanism of Action: Zinc

-  In human vaginal smooth muscle cells, zinc has a beneficial effect on the production of extracellular components produced by the muscle at 20 μ M zinc tissue level, thereby increasing the amount of collagen and elastin production and the amount of smooth muscle.¹
-  In humans, tissue zinc levels are significantly lower in patients with all types of hernia. The risk factors associated with hernia are similar to those involved in the development of prolapses.²
-  Even if there is no absolute zinc deficiency in pregnant women, the risk of peripartum and postpartum complications is still increased at a zinc level at the lower end of the normal zinc serum level range.^{3, 4, 5}
-  In a report, the effect of delivery mode (cesarean section or vaginal delivery) was studied on maternal and newborn Mg and Zn blood serum levels. While maternal Mg and Zn levels did not differ before delivery, the plasma Zn level significantly decreased in women who underwent vaginal delivery, relative to the zinc levels of women with caesarean section. This is probably due to the high stress of skeletal muscles and uterine muscles during childbirth. In another study, plasma zinc levels lower than average were associated with complications during pregnancy and during labor and delivery.^{6, 7}

1 Takacs P, Zhang Y, Candiotti K, Jaramillo S, Medina CA. Effects of PPAR-delta agonist and zinc on vaginal smooth muscle cells collagen and tropoelastin production. *Int Urogynecol J.* 2012;23(12):1775-1779.

2 Ozdemir S, Ozis ES, Gulpinar K, et al. The value of copper and zinc levels in hernia formation. *Eur J Clin Invest* 2011;41(3):285Y290

3 Schulpis KH, Karakonstantakis T, Vlachos GD, et al. Maternal-neonatal magnesium and zinc serum concentrations after vaginal delivery. *Scand J Clin Lab Invest.* 2010;70(7):465-469.


4 Lazebnik N, Kuhnert BR, Kuhnert PM, Thompson KL. Zinc status, pregnancy complications, and labor abnormalities. *Am J Obstet Gynecol.* 1988;158(1):161-166.


5 Caulfield LE, Zavaleta N, Shankar AH, Merialdi M. Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. *Am J Clin Nutr.* 1998;68(2 Suppl):499S-508S.

6 Kleopatra H. Schulpis et al. Maternal-neonatal magnesium and zinc serum concentrations after vaginal delivery. *Scandinavian Journal of Clinical & Laboratory Investigation,* 2010; 70: 465–469.

7 N. Lazebnik et al. Zinc status, pregnancy complications and labor abnormalities. *Am J Obstet Gynecol.* 1988 Jan;158(1):161-6.

Mechanism of Action: Leucine

 Numerous studies have shown leucine's beneficial role in enhancing muscle protein synthesis^{1,2}






 Leucine diet supplement in combination with resistance training showed moderately but greater changes in isometric leg muscle strength than the only physical training group.³

1 Rowlands DS, Nelson AR, Phillips SM, et al. Protein-leucine fed dose effects on muscle protein synthesis after endurance exercise. *Med Sci Sports Exerc.* 2015;47(3):547-555.

2 Luiking YC, Deutz NE, Memelink RG, Verlaan S, Wolfe RR. Postprandial muscle protein synthesis is higher after a high whey protein, leucine-enriched supplement than after a dairy-like product in healthy older people: a randomized controlled trial. *Nutr J.* 2014;13:9.

3 Trabal J, Forga M, Leyes P, et al. Effects of free leucine supplementation and resistance training on muscle strength and functional status in older adults: a randomized controlled trial. *Clin Interv Aging.* 2015;10:713-723.

Mechanism of Action: Calcium and Magnesium

-  The EFSA has approved several health claims regarding magnesium and calcium ^{1,2}.
-  Calcium and Magnesium both contribute to normal muscle function ^{1,2}.
-  Magnesium contributes to a reduction of tiredness and fatigue ¹.
-  Calcium contributes to normal neurotransmission ².
-  A combination of zinc, calcium, and magnesium supplementation may provide the necessary support for adequate muscle function ^{1,2,3}.

1 Scientific Opinion on the substantiation of health claims related to magnesium. EFSA Journal 2010;8(10):1807

2 Scientific Opinion on the substantiation of health claims related to calcium. EFSA Journal 2009;7(9):1210

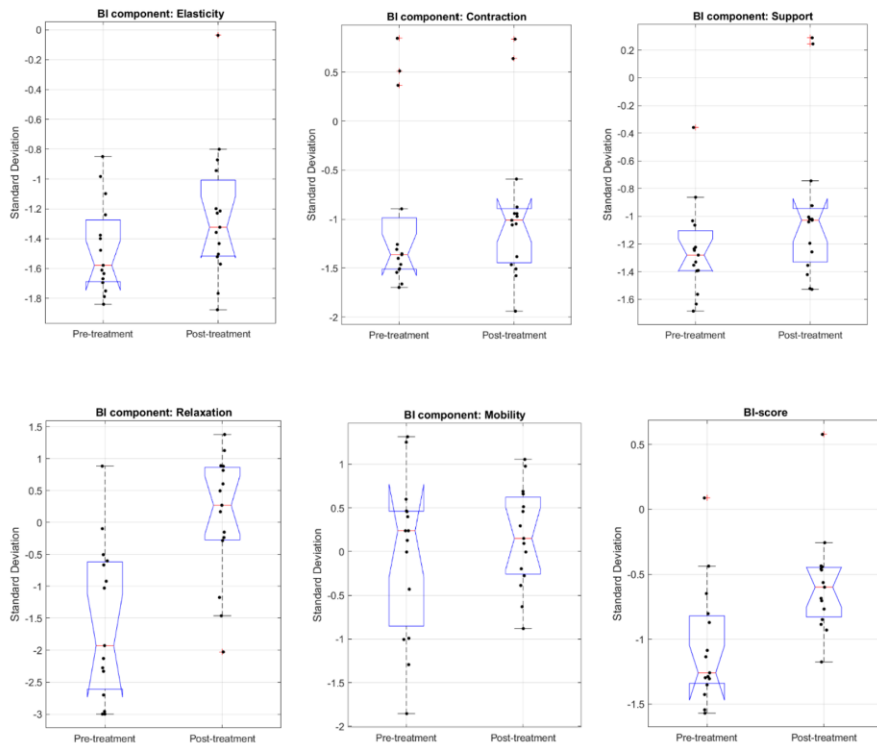
3 Scientific Opinion on the substantiation of health claims related to zinc. EFSA Journal 2009; 7(9):1229

Efficacy of INCOXIL

In order to examine the therapeutic effects of INCOXIL, a randomized double-blind clinical trial was conducted in 2023 at the Department of Obstetrics and Gynecology at the University of Debrecen in Hungary. Women with stress-predominant urinary incontinence were randomized in 1:1 ratio to receive daily oral supplementation for six weeks with either a specially formulated food supplement (treatment group) or placebo (control group). The therapeutic group was taking INCOXIL for 6 weeks, while the control group received placebo. Both groups were instructed to perform standardized daily PFMT.

Women who took INCOXIL significantly improved urinary symptoms (decrease in UDI-6 score and IIQ-7) and Biomechanical Integrity-score compared to their baseline.

Trial registration: ClinicalTrials.gov Identifier: NCT05358769



	Control Group at Baseline (N=16)	Control Group at 6 weeks (N=16)	P-value	Treatment Group at Baseline (N=16)	Treatment Group at 6 weeks (N=16)	P-value
UDI-6 score (mean ± SD)	43±18	33±26	0.22	45±21	29±21	0.02
IIQ-7 score before (mean ± SD)	48±23	40±28	0.36	50±30	30±21	0.01
Maximum vaginal squeeze pressure (cmH ₂ O, mean ± SD)	36±18	41±21	0.13	30±15	45±28	0.001
Oxford Scale (mean ± SD)	2.4±0.8	2.9±0.5	0.01	2.2±0.6	2.8±0.5	0.0005
PGI-S score (mean ± SD)	2.8±0.8	2.6±0.8	0.45	3.1±0.8	2.3±0.8	0.0001

Safety of INCOXIL

- During the clinical study there were no side effects reported at recommended doses. No serious adverse events have been reported with usage.
- INCOXIL is manufactured in a GMP complying factory and the whole product lifecycle is managed under ISO 13485 QMS and ISO 22000 food safety management system.



ISO 13485:2016



ISO 22000:2018



IP and Scientific dissemination

- ☞ The scientific foundation for product development has been summarized under the US Patent Application entitled “Pharmaceutical Composition and Method for Improving Biomechanical Integrity of the Pelvic Floor” (Submitted on 12-JAN-2023). APPLICATION NUMBER: 63438705
- ☞ We have published “A randomized controlled pilot trial to assess the effectiveness of a specially formulated food supplement and pelvic floor muscle training in women with stress-predominant urinary incontinence.” at the BMC Women's Health:

<https://bmcwomenshealth.biomedcentral.com/articles/10.1186/s12905-023-02476-z>

- ☞ INCOXIL® is a European Trademark registered by EUIPO.
- ☞ incoxil.com is a registered domain name.

Product



- INCOXIL is an instant powder dietary supplement for women performing intensive, resistance pelvic floor muscle training (PFMT) as incontinence therapy.
- Active ingredients: Creatine, Leucine, Calcium, Magnesium, and Zinc.
- 28 daily sachets are packaged in a carton box, together with an information leaflet. One sachet contains the recommended daily dose. Add one sachet of powder to 200 mL (6.75oz) of water or any other beverage. Consume after exercise.

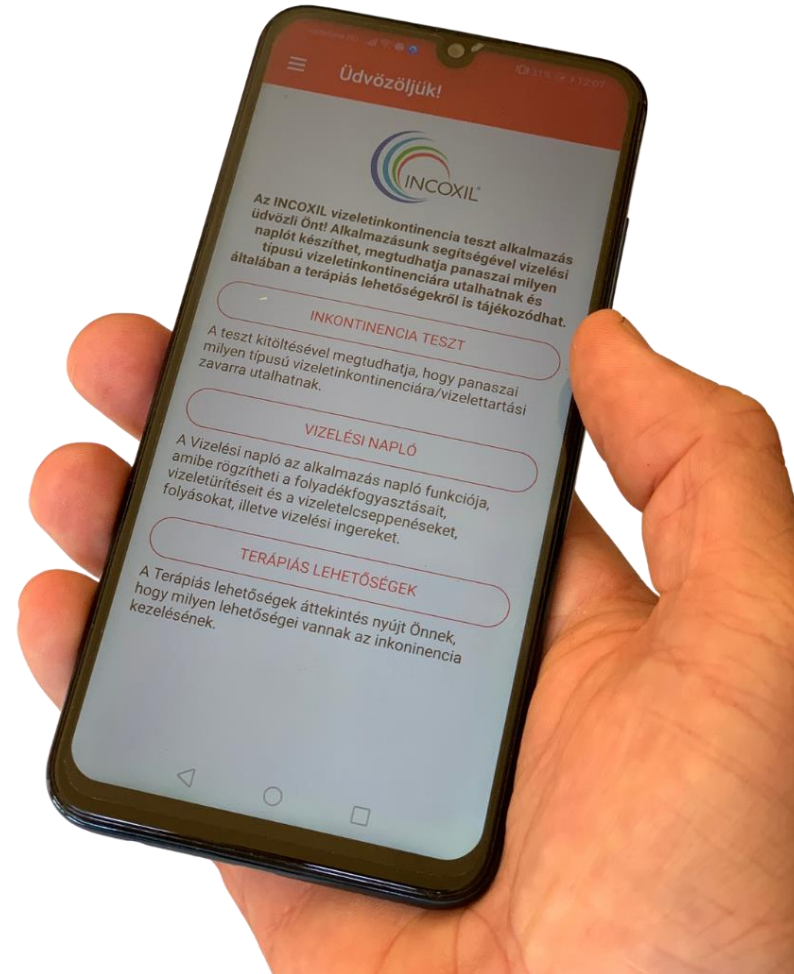
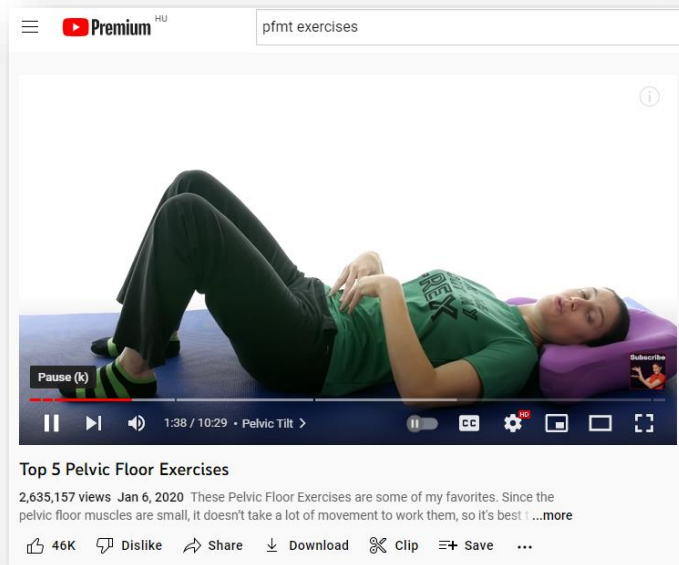
Ingredients	Amount per dose 3500mg instant drink powder	%NRV*
Creatine	3000 mg	**
L-Leucine	500 mg	**
Calcium	120 mg	15%
Magnesium	60 mg	16%
Zinc	5 mg	50%
Flavor		**

*Nutrient Reference Value.

** Nutrient Reference Value not established.

Additional services

- In cooperation with the Hungarian Society of Continence and Urogynecology we have developed an INCOXIL® app for mobile devices.
- The app is officially used in trainings for Hungarian GPs and OB-GYNs.
- Pelvic Floor Muscle Training videos can be offered with the product to help self-training.



Contact us

In person @



CPHI Milan, October 8-10, 2024, Milan, Italy

STAND 6SU32, HALL 6

Online @

<https://en.fempharma.hu>

Phone: +36 209 509 835

E-mail: zoltan.kovacs@fempharma.hu