

**Lactium**



### What dosage, and for how long?

Lactium® is taken 5 to 10 minutes before meals.

- **Acute event-related stress:** 600 mg the day before the event, 1 to 2 hours before bedtime, and 600 mg on the morning of the event.
- **Day-to-day stress:** 150 mg per day for 1 month in one single dose in the morning or 300 mg per day for 15 days in 1 or 2 doses (1 in the morning and 1 in the evening).
- **Stress-related sleep disturbances:** 150 mg per day for 1 month or 300 mg per day for 15 days in a single dose in the evening, 1 to 2 hours before bedtime.



### Appearance and duration of its effects

It has been proven that **Lactium® was active for 90 to 120 minutes after consumption by humans**. However, the actual sensation of well-being following intake of Lactium® generally appears after 1 to 2 weeks of supplementation according to the dosage.



### A high-quality bioactive ingredient

- Lactium® is produced by Ingredia, a dairy cooperative situated in northern France.
- Ingredia has been awarded ISO 9001 and FSSC 22000 certificates, and manages the food safety and traceability of Lactium® all the way through its production chain.
- Each manufacture of Lactium® is rigorously controlled: the concentration of the active peptide is determined by the HPLC method and the bioactivity verified in vivo by means of the anxiety score test (AS test).



### Lactose intolerance

Persons suffering from severe lactose intolerance may consume 7 to 12 g of lactose per day. Lactium® contains about 0.6% lactose. One dose of 150 mg Lactium® per day corresponds to 0.9 mg of lactose. **Lactose intolerant persons may therefore consume Lactium® without being concerned about potential discomfort.** Lactium® has been consumed for more than 15 years throughout the world, especially in Asia, without resulting in any reports specifically related to lactose or its origins in dairy.

### WHO SHOULD TAKE LACTIUM®, AND WHY?



Lactium may be used by all members of the family, including children and pregnant women. It is recommended for those who have difficulty managing or overcoming their stress. Lactium® may be recommended for people:

- ✓ facing occasional stressful events: a competition, job interview, medical examination, public performance, etc.
- ✓ going through a difficult and stressful period: bereavement, job loss, divorce, etc.
- ✓ experiencing symptoms linked to chronic professional or family-related stress: sleep, memory and libido disorders, mood swings, overeating, etc.
- ✓ tobacco or alcohol withdrawal
- ✓ anxiolytic drug withdrawal (consult doctor)

0 - Relaxation revolution, 2010; 1 - American Institute of Stress, 2015; 2 - Health and Safety Labour European Agency; 3 - American Psychology Association, 2014; 4 - Japanese Ministry of Health, 2014; 5 - Micio et al. 2001; 6 - poster, Nutrition 2018, Boston; 7 - Messaoudi M. et al. Eur. J. Nutr. 2004, 44 (2), 128-32; 8 - Kim J.H. et al. Eur. J. Clin. 2007, 61 (4) 536-41; 9 - A. Marreau, P.H. Marreau, Cah. Nutr. Diet., Special Edition 2005; Savaiano et al. Lactose 2006

Lactium® is an Ingredia brand



www.lactium.com

**Lactium**

## LACTIUM®, TO NATURALLY AND EFFECTIVELY MANAGE STRESS AND ANXIETY

### LACTIUM®, A NATURAL ANXIOLYTIC

- Lactium® is a **milk protein hydrolysate which contains alpha-casozepine (S1-Cn (f91-100)), a decapeptide with relaxing properties**. Lactium® originates from the trypsin hydrolysis of casein alpha S1, the main protein found in milk.
- Lactium® was patented in 1995.

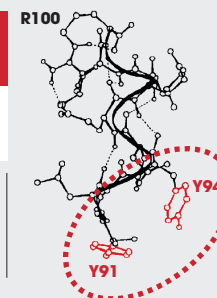
### LACTIUM®, STRUCTURE OF ALPHA-CASOZEPINE

The amino acid sequence of alpha-casozepine and its secondary structure show similarities with benzodiazepines, namely the Diazepam Binding Inhibitor (DBI), endogenous ligand of the GABA receptor:

Sequence of amino acids:  
alpha-casozepine

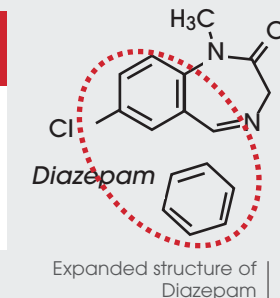
91Tyr-Leu-Gly-Tyr-Leu-Glu-Gln-Leu-Leu-Arg100

Two-dimensional structure of decapeptide by 1H-RMN (distance between two aromatic cycles close to that of Diazepam cycles)



Sequence of amino acids:  
Diazepam Binding Inhibitor

64 Thr-Ser-Lys-Glu-Asp-Ala-Met-Lys-Ala-Tyr-Ile-Asn-Lys-Val-Glu-Glu-Leu-Lys-Lys-Lys-Tyr-Gly86





## THE LACTIUM® ACTION MECHANISM

Several studies have examined the Lactium® action mechanism

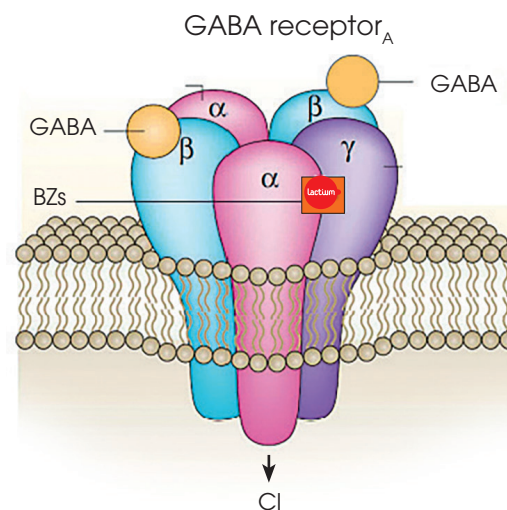
### • IN VITRO:

Lactium® has demonstrated the same effects as molecules acting on the benzodiazepine (BZD) site of the GABA receptor. Furthermore, a study<sup>5</sup> has shown the affinity of alpha-casozepine present in Lactium® with the BZD site. Alpha-casozepine has an IC<sub>50</sub> value of 88uM and a lower affinity than that of Diazepam (8.2nM).

### • IN VIVO:

The GABA receptor is an important target for modulating anxiety in animals and humans. A study has shown that in the presence of Flumazenil, an antagonist of benzodiazepines, Lactium® no longer had an anxiolytic effect in rats during the CDB anxiety test (*Conditioned Defensive Burying*)<sup>6</sup>.

• **Lactium® has an anxiolytic effect and acts, at least partially, via the GABA receptors, benzodiazepine receptors, alcohol and barbiturates.**

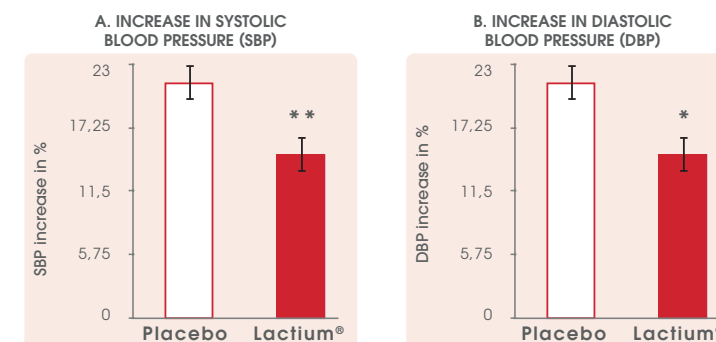


## LACTIUM®, PROVEN EFFICACY ON STRESS AND ITS EFFECTS

- **8 randomised double-blind placebo-controlled clinical studies** were conducted between 1999 and 2017 on more than 450 healthy volunteers<sup>7,8</sup>.
- They demonstrated the **efficacy of Lactium® on the reduction of stress through several physiological** (blood pressure, heart rate, cortisol levels) and **psychological** (Visual analogue scale (VAS) perceived stress) **markers**.

### PROVEN EFFICACY ON THE PHYSIOLOGICAL RESPONSE TO INDUCED STRESS (BLOOD PRESSURE)

600 mg Lactium®/day for 2 days, before mild stress induced by a psychological test followed by a physical test.



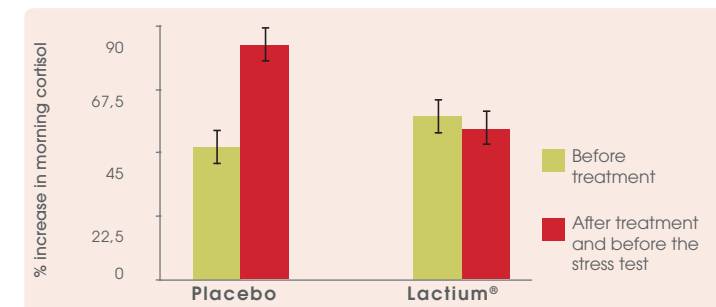
Increase in systolic (A) and diastolic (B) blood pressure after a Stroop test. The data are averages +/- standard deviation. \*\*p<0.01 \*p<0.05 (Lactium® versus placebo).

**Lactium® has an anti-stress effect at 600 mg/day for 2 days.**

Messaoudi M. et al. Eur J Nutr. 2004 44(2): 128-32

### PROVEN EFFICACY ON THE PHYSIOLOGICAL RESPONSE (MORNING CORTISOL)

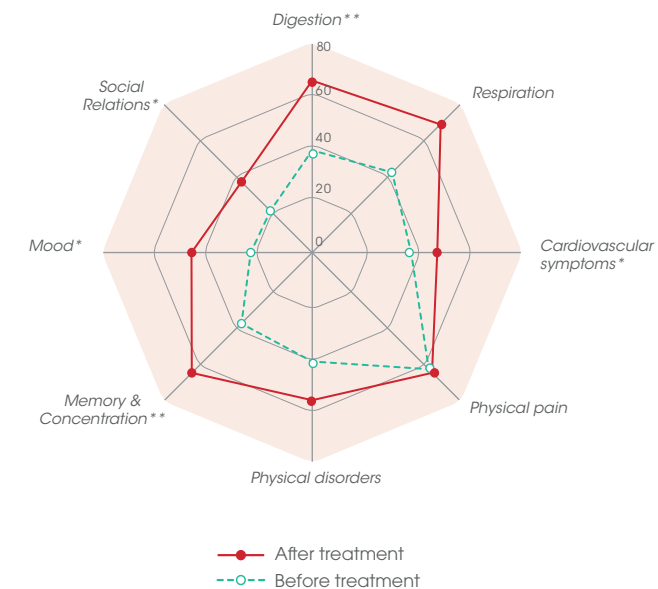
300 mg Lactium® for 30 days



**Lactium® reduces the increase in morning cortisol, a recognised bio-marker of chronic stress**

### PROVEN EFFICACY ON THE PSYCHOLOGICAL RESPONSE TO CHRONIC STRESS

150 mg Lactium®/day for 30 days in stressed women.



Percentage improvement in stress-related factors between the first day and last day of treatment.

The data are averages +/- standard deviation. \*p<0.05 \*\*p<0.01 (Lactium® versus placebo).

**Lactium® significantly reduces stress perceived in stressed women after supplementation with 150 mg/day of Lactium® for 30 days.**

Kim J.H. et al. Eur J Clin. 2007; 61(4): 536-41

## LACTIUM®, A BIOACTIVE INGREDIENT WITHOUT SIDE EFFECTS

- Lactium® is a natural ingredient whose toxicity has been evaluated according to OECD (*Organisation for Economic Co-operation and Development*) recommendations.
- Lactium® tolerance has been studied in rats and via questionnaires issued during clinical studies.
- The results have confirmed that **Lactium® does not cause any side effects**.
- **Lactium® does not cause addiction, drowsiness, or loss of memory, nor does it reduce concentration or alertness.**