

PROBENTIROX®

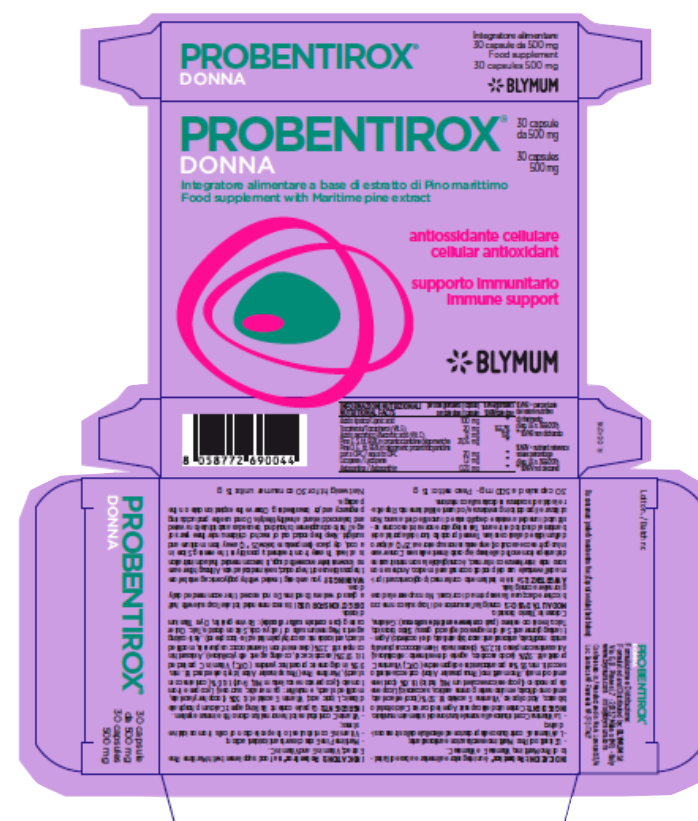
Food Supplement to Counteract
the Oxidative Stress in Dysthyroidism

Product Presentation

2021-2022

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BLYMUM is an Italian company based in Milan
providing services, products and knowledge
for those Companies specialized in developing, producing and marketing
food supplements, functional foods, novel foods, nutraceuticals, cosmetics and medical devices,
and for those Companies strategically focused on social and workplace sustainability.

Our mission
is to contribute to people's health, physical and psychological wellbeing, longevity and beauty.

smart well-being modulations



Both within our selected services and product development,

we apply the **distinctive methodology and philosophy to health, life habits correction, people's care and wellbeing improvement - Physiological Balance Management.**

It is mindset, structured and customized under the brand **Livella®** and it is based upon the idea that wellness and health are given by a specific physiological balanced status of the human organism.

health, life habits, and smart well-being departments

BLYMUM SERVICES AND PRODUCTS

SERVICES

SERVICES

BLYMUM offers professional support

to Pharmaceutical, Food, Healthcare and other Clients in the following areas:

Clinical Trials Management; Regulatory Compliance; Wellbeing Management; Sustainable Impact Modeling; Change Management & Mentoring.

PRODUCTS

PRODUCTS

In parallel, we are directly involved in product innovation processes.

The BLYMUM distinctive feature lies in the development of Physiological Modulators, that are scientifically proven solutions for specific human psycho-physical problems, pathological phenomena and adverse living and working conditions:

BLYMUM Food Supplements; On-demand Formulation Development.

THE NEW PRODUCT FOR THE OXIDATIVE STRESS IN DYSTHYROIDISM

- In terms of products, the distinctive company's competency lies in the development of **Physiological Modulators** that ensure health, avoid preventable diseases and undertake a balanced state of body and mind.
- In particular, BLYMUM is developing and proposes different types of Physiological Modulators, such as **Food Supplements, Novel Foods, Functional Foods, Cosmetics and Nutraceutical Products**.
- BLYMUM has introduced on the market:



MAIN BENEFITS OF PROBENTIROX®

Problem Solving:

PROBENTIROX® is a Food Supplement, indicated for
reducing the oxidative stress and side effects
ascribable to the treatment with levothyroxine.

Its composition is highly tolerated by individuals affected by hypothyroidism, and it
significantly contributes
to the overall psycho-physical well-being of women.

Target:

Females

PROBENTIROX[®] INNOVATION

GRANTED BY THE EUROPEAN PATENT OFFICE



(11) **EP 2 441 450 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
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A61K 31/353 (2006.01) **A61K 31/355** (2006.01)
A61K 31/385 (2006.01) **A61K 9/48** (2006.01)
A61P 5/14 (2006.01)

(21) Application number: **10425334.9**

(22) Date of filing: **18.10.2010**

(54) **Antioxidant composition for reducing the oxidative stress and side effects ascribable to treatment with levothyroxine**

Antioxidanszusammensetzung zur Reduzierung von oxidativem Stress und der Nebenwirkungen, die auf die Behandlung mit Levothyroxin zurückzuführen sind

Composition antioxydante pour réduire le stress oxydatif et les effets secondaires attribuables à un traitement avec la lévothyroxine

(84) Designated Contracting States:
**AL AT BE BG CH CY CZ DE DK EE ES FI FR GB
GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO
PL PT RO RS SE SI SK SM TR**

• **BRUNO A N ET AL: "Activation of adenosine A1 receptors alters behavioral and biochemical parameters in hyperthyroid rats", BEHAVIOURAL BRAIN RESEARCH, ELSEVIER, AMSTERDAM. NL. vol. 167. no. 2. 28 February**

LEADING ADMINISTRATION CONDITIONS

Adverse Events Report in Patients Treated with Levothyroxine [Hennessy Jv et Al Endocr Pract 2010;16:357]

- Nodular thyroid disorders are the most common endocrine disease. The prevalence of this disease is between 4 - 7% of the population and increases with age, reaching up to 50% of cases by age 60.
- In patients with thyroid insufficiency, therapy involves administration of L-T4. This is actually a substitute treatment, with the patient consuming the amount of hormone which the body cannot produce itself. The initial dose is small and is then gradually increased until the appropriate dose is reached.
- L-T4 is absorbed in a variable and incomplete manner that is the root of the problem of oxidative stress: a wave of oxidative stress is generated daily with a peak between two and four hours after administration of L-T4.
- In addition, it has been found that thyroid hormone administration not only consistently generates oxidative stress, but also a number of side effects such as anxiety, agitation, sweating, palpitations and headaches. Often, these side effects are such as to be disabling to the normal performance of daily activities by the individual.

PROBENTIROX® FORMULATION AND PROPERTIES

- PROBENTIROX® is a Physiological Modulator comprising oligomeric proanthocyanidins, lipoic acid, vitamin E, vitamin C, lycopene and astaxanthin. It has been found that the synergistic combination of these components reduces significantly the oxidative stress associated with levothyroxine consumption, acting in parallel:
 - Oligomeric proanthocyanidins (OPC) are used against inflammation
 - Lipoic acid contributes to mitochondrial protection
 - Vitamin E and astaxanthin protect DNA, proteins and lipids from oxidative damage
 - Lycopene protects the body from circulating reactive cells

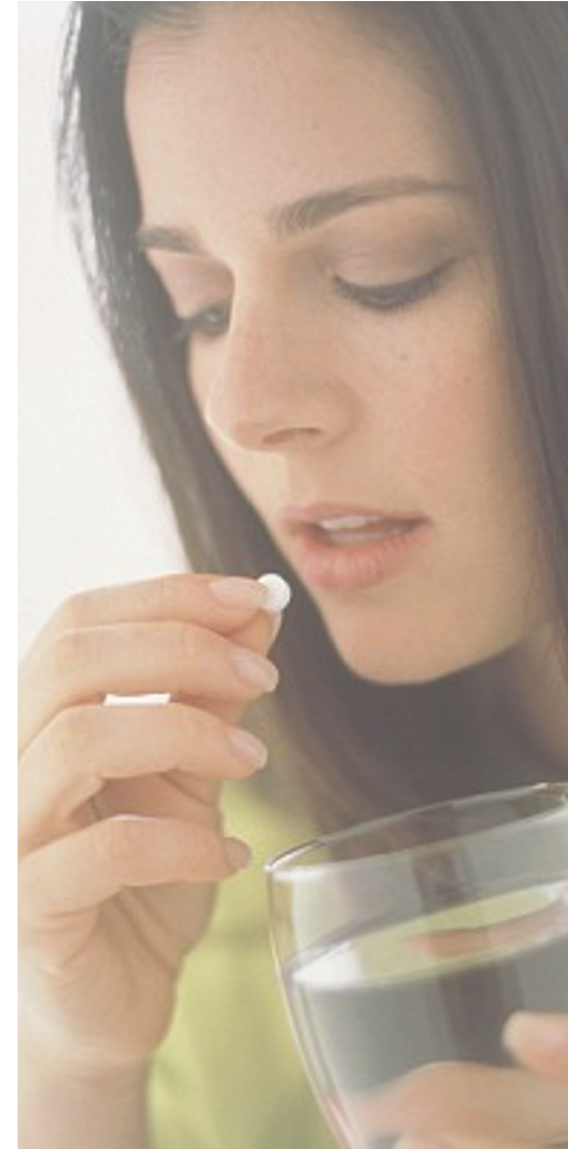
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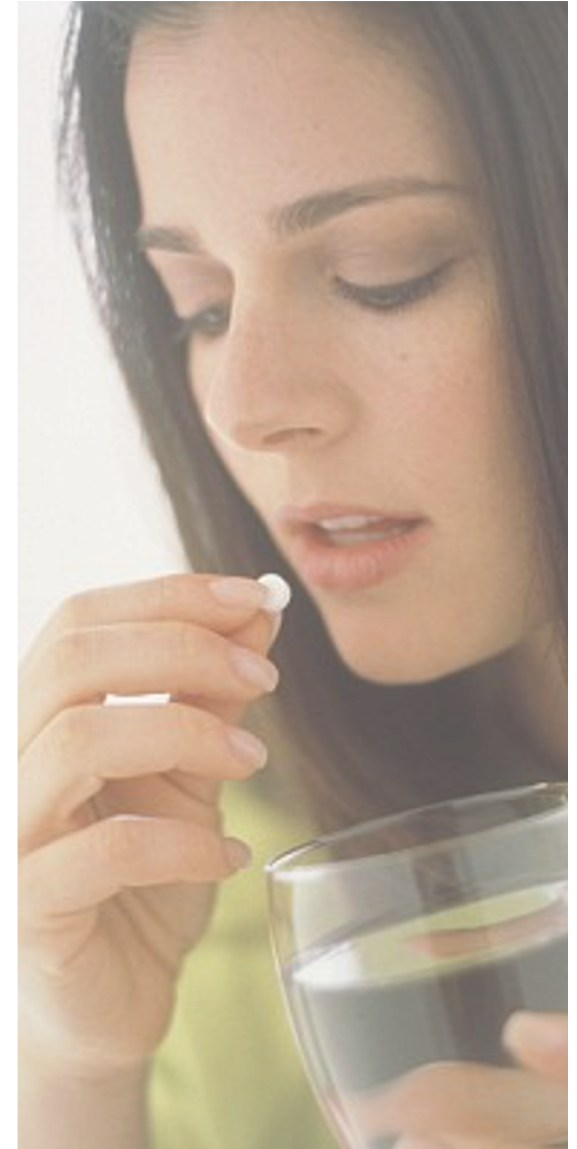
PROBENTIROX®

CLINICAL TRIAL “A”
OS IN PRIMARY HYPO FOLLOWING LT4 TREATMENT
[Cornelli U et Al Pan Med 2011;53:95]

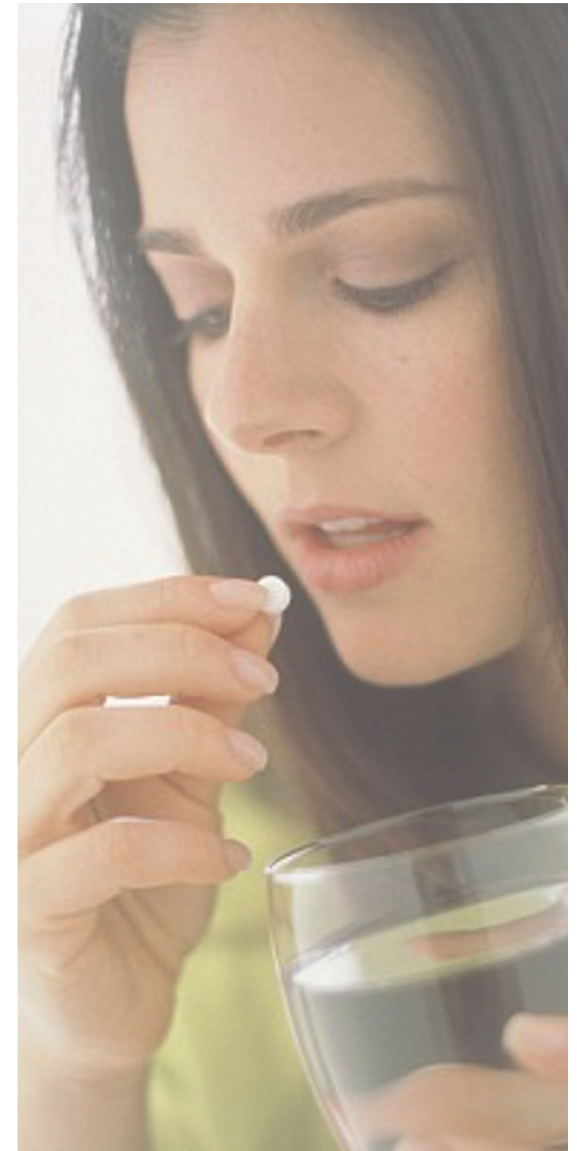
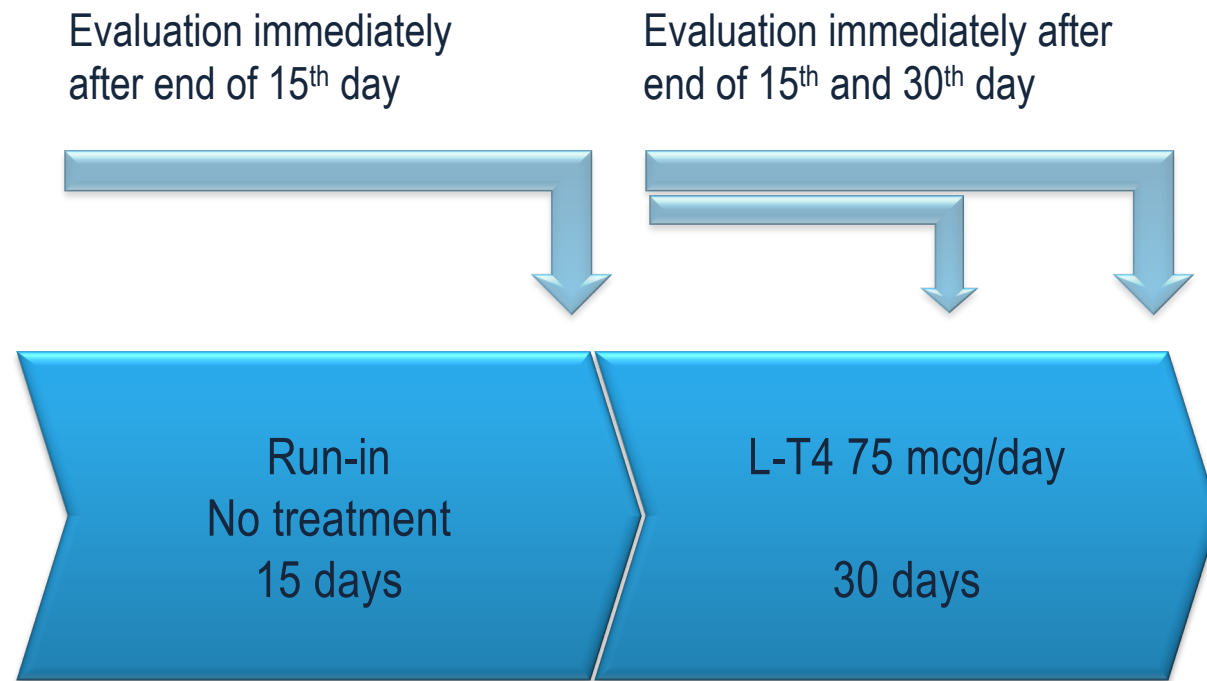


GENERAL DESCRIPTION

- **Sample**
 - 36 patients (16 M/20 F)
 - age 41-61 affected by hypothyroidism
 - non hormonal replacement therapy in case of menopause
- **Symptoms**
 - Anxiety/agitation, sweating, palpitations headache, daily discomfort, oxidative stress (d-ROMs test), HsCRP (as inflammatory index)
- **Lab analysis**
 - T3, T4, TC, TG, d-ROMs, CRP
- **Treatment**
 - with a fixed dose of 75µg LT4



TIME TABLE



RESULTS

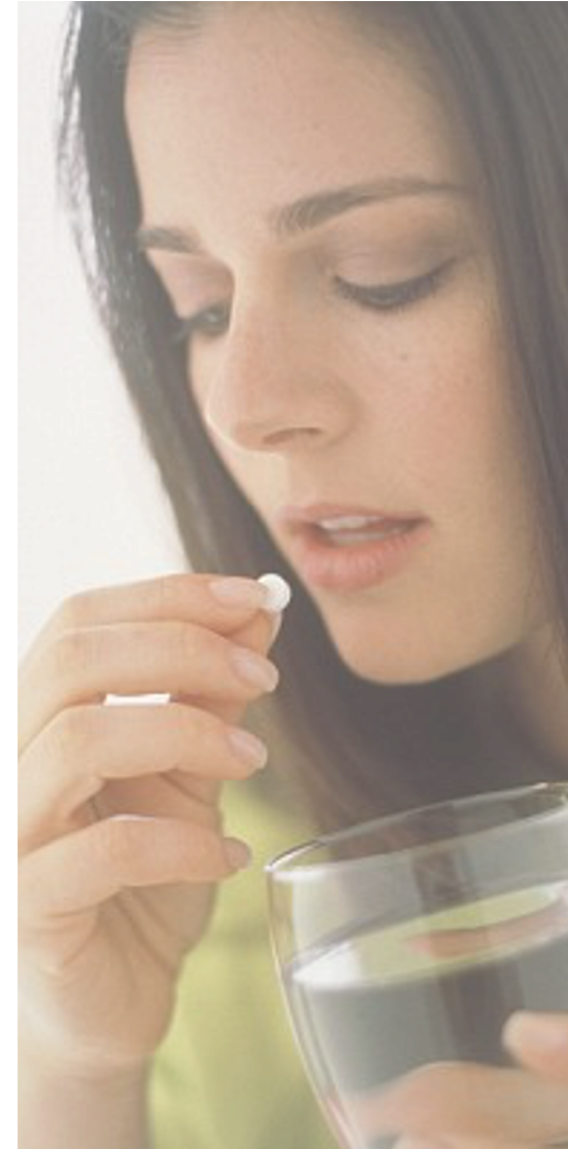
Variables	Measure	-15 – 0 days	0 – 15 days	16 – 30 days
T4	µg/mL	2.5 ± 0.71	9.4 ± 1.94	14.6 ± 2.13
T3	ng/mL	58 ± 12.4	97 ± 10.7	168 ± 17.8
TSH	µU/mL	91 ± 10.6	28 ± 9.7	8 ± 2.8
d-ROMs	Carr.U.	370 ± 27.7	425 ± 34.6	435 ± 39.5
HsCRP	mg/L	3.2 ± 1.32	3.6 ± 1.24	4.0 ± 1.27
A/Agitation	15 days I	0.3 ± 0.56	13.6 ± 1.25	13.6 ± 1.28
Sweating	15 days I	0.3 ± 0.44	9.6 ± 1.14	10.9 ± 2.12
Palpitation	15 days I	0.2 ± 0.51	14.1 ± 0.93	14.1 ± 1.15
Headache	15 days I	0.4 ± 0.50	12.2 ± 1.64	11.9 ± 1.96
Daily disc.	days	0.5 ± 0.66	3.8 ± 0.75	4.8 ± 0.78



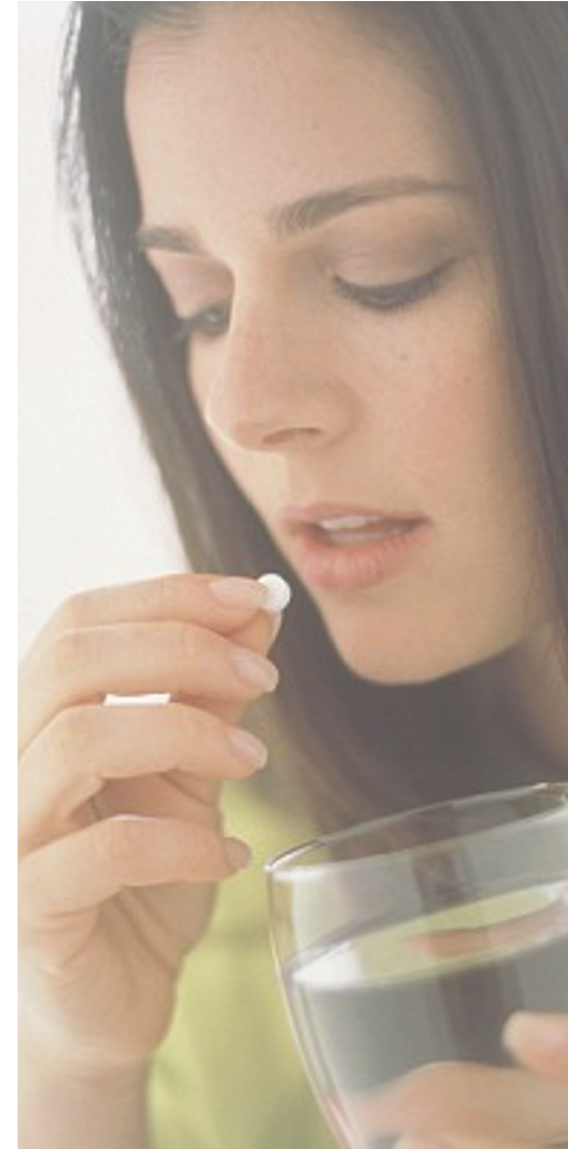
CONCLUSIONS

**The 30 days treatment of LT4
in patients suffering from hypothyroidism
causes side effects due to OS**

**The increase of HsCRP
witnesses a worsening
of the inflammatory condition**

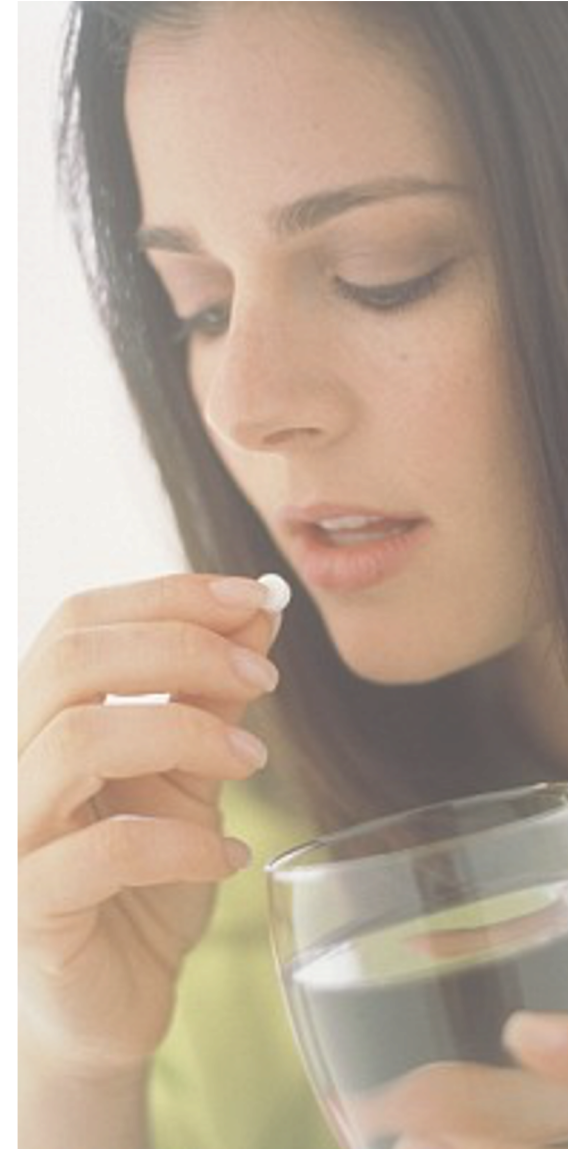


CLINICAL TRIAL “B”
CLINICAL PHARMACOLOGY
by
Prof. Umberto Cornelli MD PhD DrScHC,
Loyola University School of Medicine - Chicago

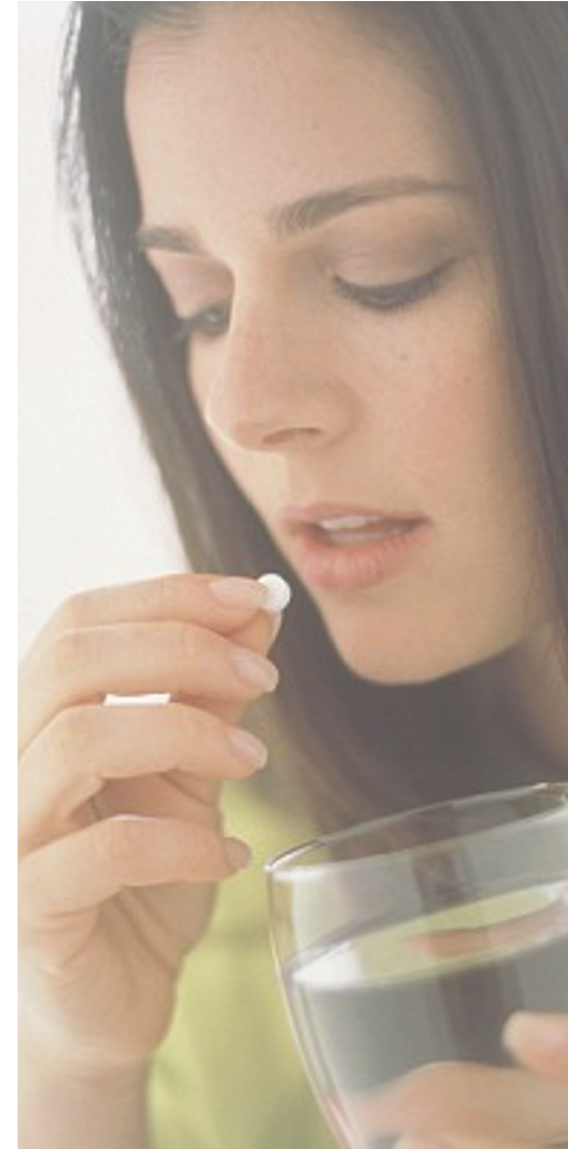
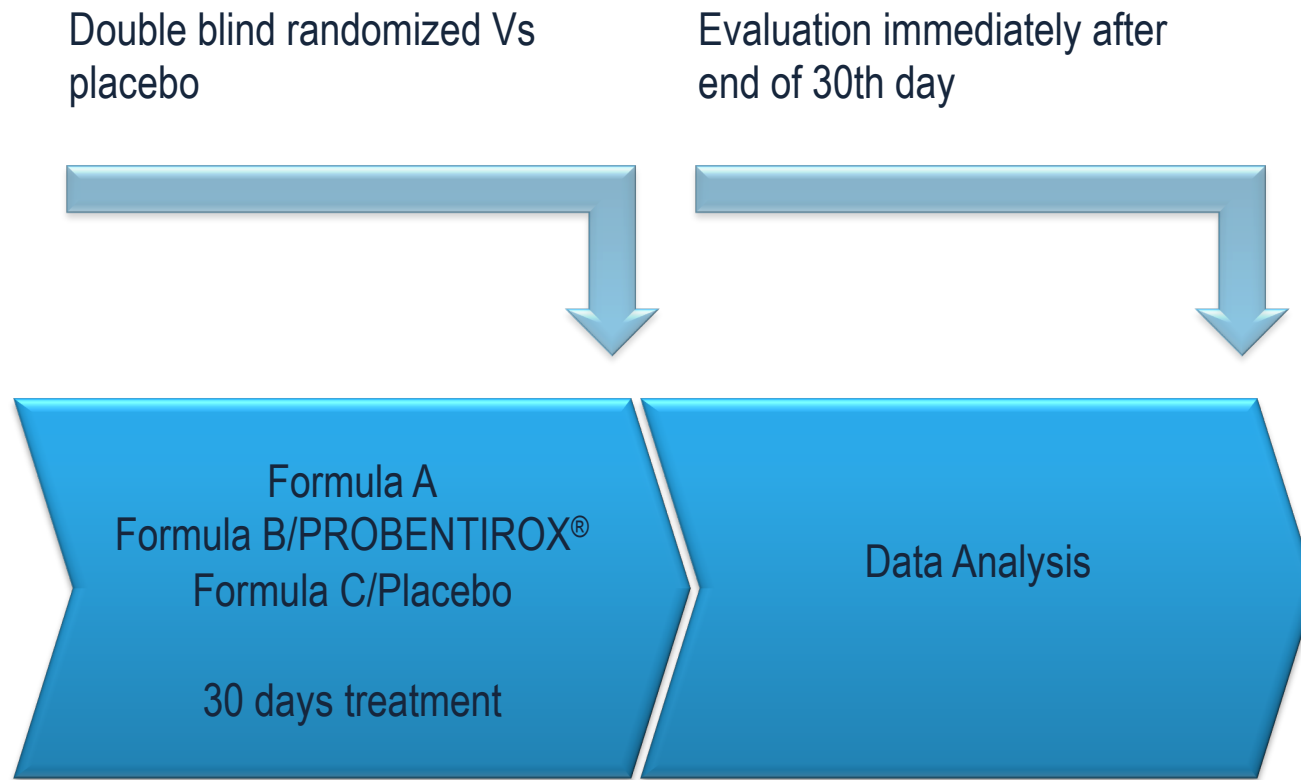


GENERAL DESCRIPTION

- **Sample**
 - Three groups of 10 patients (M/F) starting therapy with LT4 for hypothyroidism at 75 µg/day
 - Each group administered with different formulations A, B, and C (as follows)
 - In females the treatment with HRP (hormonal replacement therapy) or with any antioxidant supplement therapy were among exclusion criteria; all other concomitant therapies were allowed provided at the same dosage through the experience
- **Methodology**
 - 30 days treatment double blind randomized
 - 1 cps/day



TIME TABLE



FORMULATIONS

FORMULA A:	
Components	mg/capsule
Astaxanthin 2,5%	0,25
Bioflavonoids from citrus	33,0
Lycopene 6% (from tomatoes)	1,2
Calcium lactate	358
Calcium carbonate	221
Vitamin D3	mcg 2.5
Total	613,70

FORMULA B:	
Component	mg/capsule
Pine bark extract tit. 95%	
OPC	21,05
Lipoic acid	100,00
Vitamin E acetate 50%	85,13
Ascorbic acid protected 97,5%	12,00
Lycopene 6% (from tomatoes)	26,00
Astaxanthin 2,5%	13,00
Micronized silica USP	5,00
Calcium phosphate dibasic	124,82
Talc	5,00
Magnesium stearate	10,00
Hard white gelatine capsule size 0	98,00
Total	500.00

FORMULA C:	
Component	mg/capsule
Arabic gum	200
Total	200.00

BASELINE VALUES

BASELINE VALUES				
Variables	Groups			ANOVA
	A [Formula A]	B [Formula B]	C [Placebo]	
Age [years]	53 ± 5.6	54 ± 3.9	54 ± 6.0	A = B = C
Sex	5 M 7 F	5 M 7 F	5 M 7 F	
BMI [Kg/m ²]	27.1 ± 1,49	27.7 ± 1,58	27.6 ± 1,73	A = B = C
d-ROMs [Carr.U.]	373 ± 36.1	384 ± 39.1	376 ± 24.0	A = B = C
T4 [µg/dL]	3.0 ± 0.99	3.3 ± 0.66	3.2 ± 0.84	A = B = C
T3 [ng/dL]	50 ± 6.7	52 ± 8.2	51 ± 9.5	A = B = C
TSH [µU/dL]	110 ± 20.4	102 ± 27.8	117 ± 17.7	A = B = C
hs-CRP [mg/L]	3.8 ± 1.41	3.4 ± 1.34	3.6 ± 1.03	A = B = C
Anx/agit [I]	0.6 ± 0.51	0.5 ± 0.52	0.6 ± 0.51	A = B = C
Sweating [I]	0.4 ± 0.51	0.3 ± 0.49	0.5 ± 0.52	A = B = C
Palpitations [I]	0.3 ± 0.49	0.6 ± 1.00	0.2 ± 0.39	A = B = C
Headache [I]	0.3 ± 0.62	0.5 ± 0.52	0.2 ± 0.39	A = B = C

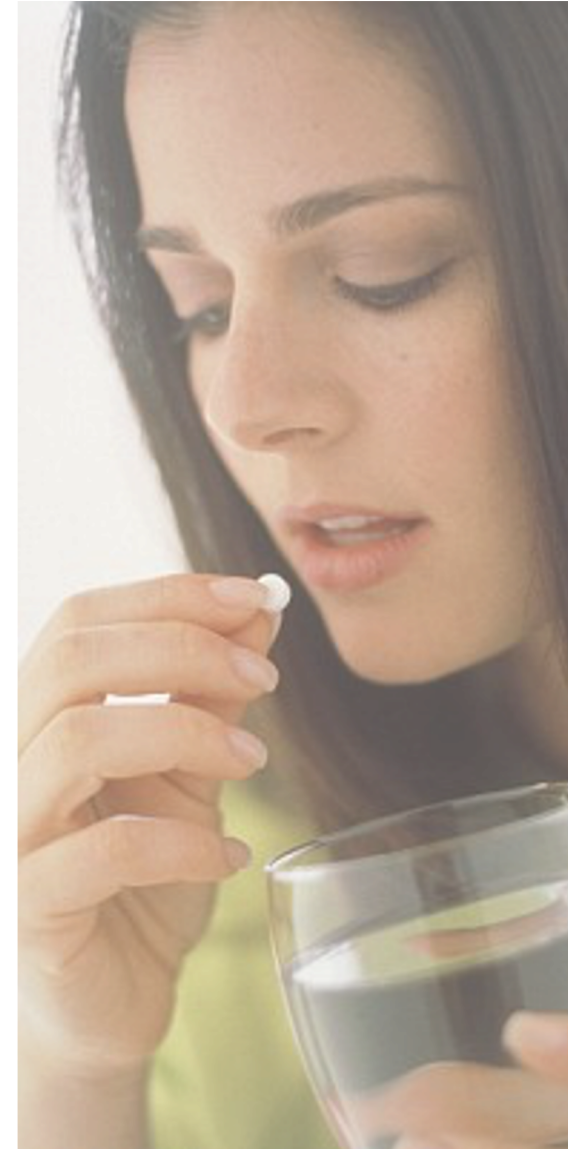
RESULTS

FOLLOWING 30 DAYS TREATMENT

Variables	A	B	C	ANOVA
d-ROMs [Carr.U.]	312 ± 21.0	273 ± 24.3	409 ± 31.7	C > B > A
T4 [µg/dL]	10.7 ± 1.41	11.2 ± 2.16	11.7 ± 2.97	A = B = C
T3 [ng/dL]	171 ± 11.6	162 ± 18.8	176 ± 14.9	A = B = C
TSH [µ U/dL]	2.5 ± 0.82	2.6 ± 0.53	2.2 ± 0.84	A = B = C
hs-CRP [mg/L]	3.8 ± 1.31	3.2 ± 0.99	4.4 ± 0.88	C > A > B
Anx/agit [I]	10.2 ± 1.34	0.6 ± 0.67	10.7 ± 1.67	C = A > B
Sweating [I]	7.9 ± 1.20	0.7 ± 0.89	10.7 ± 1.97	C > A > B
Palpitations [I]	8.6 ± 2.54	0.6 ± 0.67	12.3 ± 1.60	C > A > B
Headache [I]	7.3 ± 1.67	0.8 ± 1.14	12.3 ± 1.50	C > A > B
Daily disc [30 d]	4.1 ± 0.90	1.3 ± 0.62	6.2 ± 0.72	C > A > B

CONCLUSIONS

**To reduce and counteract
the oxidative stress deriving
from treatment with LT4,
particular ad hoc
Physiological Modulators
are needed**



SCIENTIFIC PUBLICATIONS

Activity of a Combination of Physiological Modulators in Limiting Side Effects in Patients Suffering from Primary Hypothyroidism during Levothyroxine Treatment (U. Cornelli, A. Ledda, G. Belcaro and A. Finco)

<http://www.blymum.com/contents/files/PAPER-PROBENTIROX-AUSTIN.pdf>

Activity of Some Physiological Modulators In Reducing the Side Effects of Levothyroxine in Patients Suffering from Primary Hypothyroidism (U. Cornelli, G. Belcaro, A. Ledda, B. Feragalli)

<http://www.blymum.com/contents/files/PAPER-PROBENTIROX-PH.MODULATORS.pdf>

Oxidative Stress Following Administration of Levothyroxine in Subjects Suffering From Primary Hypothyroidism (U. Cornelli, G. Belcaro, A. Ledda, B. Feragalli)

<http://www.blymum.com/contents/files/PAPER-PROBENTIROX-OS.pdf>

PROBENTIROX® ON THE MARKET

- Box of 30 capsules 500 mg each
- Administration: 1 capsule/per day
- WARNINGS: Although there are no known interferences with medications or hormone replacement therapy, it is recommended that administration is at least 1h away from therapies, possibly in the evening. Store in a cool, dry place at room temperature and away from sunlight. Keep this product out of reach of children under three years of age. Dietary supplements are not intended as a substitute for a varied and balanced diet and a healthy lifestyle. Do not use this product during pregnancy and/or lactation. Observe the expiration date printed on the package. Side effects: no known side effects due to the assumption of Probentirox®.

CLAIMS



PACKAGING



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