

# NOTEBOOK DATA COLLECTION STUDY:

|| Effectiveness and tolerability of Contrurine Plus in the treatment of  
Overactive bladder in women ||

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## Authors.

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## **FOR EACH PATIENT:**

### Annex I.

- Patient Information.
- Informed Consent.
- Letter of commitment from the principal investigator.

### Annex II documents to be completed in the study.

- Sheet 1. Sheet overall data collection.
- Sheet 2-1. Questionnaire OABq-SF. Symptomatology. Pretreatment.
- Sheet 2-2. Questionnaire OABq-SF. Quality of life. Pretreatment.
- Sheet 2-3. Questionnaire OABq-SF. Symptomatology. Post-treatment.
- Sheet 2-4. Questionnaire OABq-SF. Quality of life. Post-treatment.
- Sheet 3. Summary Sheet.

## Introduction.

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Urinary incontinence was defined in 1988 as a condition in which the loss of urine is a social/hygienic problem objectively demonstrable. In 2003 ICS replaced it with the complaint of any involuntary loss of urine<sup>1</sup>.

Overactive bladder (OAB) is considered, the presence of urinary urgency, usually accompanied by increased urinary frequency (more than 8 times/24 hours), and night-time (more than once/night), with or without urinary urge incontinence, in the absence of a urinary tract infection (UTI) or other pathologies<sup>2</sup>.

The presence of overactive bladder is more common in females (8 % -42 %), than in the male (10 % -26 %), frequently causing urinary incontinence<sup>2</sup>.

The storing and emptying of urine by the lower urinary tract, depends on the activity of the smooth and striated muscles in the urinary bladder, urethra and the external urethral sphincter. This activity is controlled by neuronal circuits in the brain, the spinal cord and the peripheral lymph nodes. Several neurotransmitters (acetylcholine, norepinephrine, dopamine, serotonin, excitatory and inhibitory amino acids, adenosine triphosphate, nitric oxide, and neuropeptides), play a role in the regulation of the lower urinary tract.

Many neurons used acid  $\gamma$ -amino butyric acid (GABA) and glutamate as neurotransmitters. GABA and glutamate receptors regulate the excitability of many neuronal circuits (GABA is an inhibitory neurotransmitter, while glutamate is an exciter) remain actively involved in important pathophysiological processes. Drugs that increases the inhibitory events of GABA, they decreases excitatory events regulated by glutamate.

In the central nervous system, glutamate is one of the major excitatory amino acids, while the acids glycine and  $\gamma$ -amino butyric acid (GABA) are the main neurotransmitters inhibitors. They act to inhibit the reflection of urination at the supraspinal and spinal cord locations.

Given that, in the composition of the **Contrurine Plus** we find gabaergic precursors, the aim is to study the possible action of this compound in the **urinary incontinence by overactive bladder**.

Another of the components are the proanthocyanidins (PAC's), extracted from the grape seed (*Vitis vinifera*, 95% pure) and are of the same type as the "proanthocyanidins," from the American red cranberry. They are very useful for the prevention of urinary tract infections and have properties of antiadhesion of uropathogenic bacteria, already as sensitive or resistant to antibiotics. These PAC's inhibits the synthesis of the fimbriae P and induces a bacterial strain<sup>3</sup>.

OAB has been associated with urinary tract infections, *Rees et al.* described a 25% of detrusor overactivity in recurrent cystitis, and *Moore* found a significant association between hyperactivity detrusor and bacterial cystitis. Also, *Bhatia and Bergman* checked, in their series, a drop from 50% of cases of OAB in women with bacteriuria, post-treatment of the infection<sup>4</sup>.

*Lapides and Costello* describes that elevated pressures of the detrusor, above all, in the form of involuntary detrusor contractions, could compress the bladder wall, resulting in ischemia which would promote the bacterial cystitis.

This is why **Contrurine Plus**, by their two fundamental components: GABAergic precursors and proantocianidinas, will become a dual therapy, useful, in the OAB in women.

## Objective.

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Assess the effectiveness of **Contrurine Plus** in the treatment of **patients with overactive bladder**. **A capsule each day, before bedtime, for 3 months**.

## Inclusion criteria.

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Women with overactive bladder.

## Exclusion criteria.

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Refusal on the part of the patient to enter the study or inability to complete the treatment for some contraindications, as well as current active urinary tract infection.

## Methodology.

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It will be assessed; both the degree of symptomatology, with or without urge incontinence, as well as its relationship with their life's quality before and after treatment, in order to establish, in their case, if there is any significant variation.

It has included a specific questionnaire for overactive bladder (OABq-SF), which consists of 2 parts: the first is dedicated to the symptomatology with 6 questions and the second to the quality of life with 13 questions<sup>5</sup>.

There will be also a summary with the data obtained from each patient. In the **annex I**, it includes the patient information, informed consent, and the letter of commitment from the principal investigator. While in the **Annex II**, it can be found the overall data collection sheet, side effects, OABq-SF, and the summary sheet.

## References.

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1. Maximal flow BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA) /International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol*. 2010; 21:5-26.
2. Frank A, Espuña M. female urinary incontinence. In: practical guides in urology. Salinas J (Ed). Elsevier Doyma pub. Madrid 2011.
3. Gabetta B, Fuzzanti N, Griffini TO et al. Characterization of proanthocyanidins from grape seeds. *Phytotherapy*. 2000; 71:162-175.
4. Bhatia NN, Bergman A. Cystometry: unstable bladder test and urinary tract infection. *Br J Urol*. 1986; 58(2): 134-137.
5. Staskin D, Kellher C: Initial assessment of urinary incontinence in adult male and female patients. In incontinence. P. 366. Ed. Abrams et al. 5th edition. 2013.

# PATIENT IDENTIFIER



# Annex 1.

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## PATIENT INFORMATION.

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Participation of women patients with overactive bladder in the study "**Effectiveness And tolerability of Contrurine Plus in the treatment of overactive bladder in women**".

### PURPOSE OF THE STUDY

The **Contrurine Plus** is a product classified as a food supplement that has no toxicity effects, since the formula of the product contains some very small concentrations of the active principles.

The study of the **Contrurine Plus** in adults with urinary control problems will make it possible that, using the output produced by Laboratec S. L., you can and/or learn how to control the volumes of urine. This may involve a break for you and a well-being for those around you, thus increasing the confidence in yourself.

In order for you to decide whether you want to be part of this project, you must understand the advantages of the same to be able to take a decision in this regard. This process is what is known as informed consent.

This informed consent gives detailed information about the project and besides, your doctor will discuss with you this information so you can understand it. Once you understand the project you will be asked to sign the informed consent if you want to participate in it. You will be given a copy of this document to be able to save it. Participation in this project is voluntary.

### RISKS ASSOCIATED WITH THE PROJECT

Toxicity studies of the product have shown that the patient runs no risk derived from the manipulation of the material, unless you have allergy to any of the components of the product, in which case a doctor should be consulted.

### BENEFITS ASSOCIATED WITH THE PROJECT

The social benefits that can be generated for the achievement of this project are numerous: currently there is an increasing incidence of adults with overactive bladder, without notable pathologic complications, but with considerable psicologic and emotional complications. These already are medical conditions that would require the advice of your doctor. **Contrurine Plus analysis can help:**

1. The well-being of the adult and the psychological improvement.
2. To alleviate the social problem, because the adult person would feel good about herself and, in this way you have greater interaction with the society.
3. To the domestic tasks related to this problem.

You can request the researcher more information about the project.

## PERMISSION TO REVIEW YOUR DATA / CONFIDENTIALITY

Your identity and all the data relating to your personal information will be kept confidential, unless requested otherwise by law. It will not be published any information that could identify you in any reports or publications resulting from this project. Granted access will be allowed for the review of the records to the medical ethics committee and the Health Authorities in case of requesting it. By signing this confidentiality letter, you declare that you agree with this document.

Your data will be protected by Law 15/1999 on *Protection of Personal Data*.

## BENEFITS

For you there will be no direct monetary benefit by participation in this project. You will collaborate voluntarily in the participation of this research project.

## INVESTIGATOR RESPONSIBLE FOR INFORMING THE PATIENT

The person in charge of informing patients of the opportunity to be part of the study to analyse the effects of **Contrurine Plus** will be the principal investigator Mr/Mrs: ... ..  
... ..

## COMPLETED BY THE PATIENT AND INVESTIGATOR

# INFORMED CONSENT

Researcher Identifier:

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Patient Identifier:

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Title of the project "**Efficacy and tolerability of Contrurine Plus in the treatment of overactive bladder in women**".

I ... .. declare under my responsibility that I have read the information sheet of the patient about the project and I agreed to participate in this research project in the service of ... .. Hospital ... .., under the supervision of ... ..

It has handed to me a copy of the patient information sheet. It has been explained to me so that I am going to be recruited and the benefits that can derive from this study. I have been given time and opportunity to ask questions. All questions were answered to my satisfaction.

I know that it will be kept confidential my identity because I will be identified with a numeric code. The data gathered will use to verify if the **Contrurine Plus** has a positive or a negative effect on the retention of urine in the overactive bladder. It has been explained to me that the number of adults involved in this project will be a representative sample, that the active principles of **Contrurine Plus** could possibly be investigated more thoroughly, but that it is not the purpose of this study.

I give my voluntarily consent to be able to carry out the project related with the **Contrurine Plus**, which is an extract from grape seeds of *Vitis Vinifera*, non-protein amino acid (GABA), flavonoids (Rutin), vitamin B<sub>6</sub> and omega 3 and that has no side effects, unless that I am allergic to any of the components.

In \_\_\_\_\_ to \_\_\_\_\_ of \_\_\_\_\_ of 20 \_\_\_\_\_

Signature of the patient:

Signature of the principal investigator (PI):

Name.....

Service of .....

Hospital .....

*I, as the principal investigator, found that I have explained the characteristics and the objective of the project and potential benefits to the patient. The patient is part of the research study through its dated signature in person.*

## LETTER OF COMMITMENT FROM THE PRINCIPAL INVESTIGATOR

I .....

From Service of .....

From Hospital .....

I certify that:

- I know that and agreed to participate as a main principal investigator in the study entitled: **"Efficacy and tolerability of Contrurine Plus in the treatment of overactive bladder in women"**, and I am committed to ensure that the data from each subject is treated and controlled in accordance with the Protocol approved by the Ethics Committee of Clinical Research and in his absence, by *law-15/1999 from Data Protection Act*.
- That complies with the ethical and legal standards applicable to this type of study and will abide by the *standards of Good Clinical Practice* and Laboratory in its realization.

In \_\_\_\_\_ to \_\_\_\_\_ of \_\_\_\_\_ of 20 \_\_\_\_\_

**Signature:**

# Annex II.

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## SHEET 1. GENERAL SHEET DATA COLLECTION.

Researcher Identifier:







Patient Identifier:






Age:  Sex: Male ☐ Women ☐Size:  Height:       CmBMI:  EAP (pregnancies, abortions, stillbirths): ☐ Yes ☐ NoDystocia in childbirth: ☐ Yes ☐ NoInterventions: ☐ Yes ☐ NoMenopause: ☐ Yes ☐ No

Current treatments .....

Previous incontinence treatments .....

Other relevant background .....

Starting date of treatment   /   /     Completion date of treatment:   /   /     

Dose.....

Compliance with treatment: ☐ Yes ☐ NoInterrupt treatment: ☐ Yes ☐ No

Reason for discontinuation of treatment (if occurred):

☐ Side effect☐ Lack of improvement☐ Study Completion☐ Decision of the patient (specify) .....

# COMPLETED BY THE PATIENT

## SHEET 2-1. QUESTIONNAIRE OABq-SF ON OVERACTIVE BLADER.

Researcher Identifier:

Patient Identifier:

### PRE-TREATMENT

### SYMPTOMATOLOGY

In this questionnaire you will find questions on how much you have been annoyed about certain symptoms of the bladder during the last 4 weeks. Mark a ✓ or ✗ in the box that best describes how annoying are each symptom during the last 4 weeks. There is no right or wrong answers. Ensure to respond to all questions.

During the last 4 weeks, how much did it annoy to...?		Nothing	A little	Something	Much	Very Much
1	have wishes to urinate?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
2	have sudden desires to urinate with little or no notice?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
3	have accidental loss of small amounts of urine?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
4	have to urinate at night?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
5	wake up in the night because had to urinate?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
6	have loss of urine associated with a strong desire to urinate?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5

# COMPLETED BY PATIENT

## SHEET 2-2. QUESTIONNAIRE OABq-SF ON OVERACTIVE BLADDER

Researcher Identifier:

Patient Identifier:

### PRE-TREATMENT

### LIFE QUALITY

In the following questions, think about the general symptoms of your bladder during the last 4 weeks and the impact they have had on your life. Answer each question as best as possible indicating the frequency with which you have felt it. Mark a ✓ or ✗ in the box that best respond to each question. Ensure to answer to all the questions.

During the last 4 weeks, how often, due to your bladder symptoms...		Never	Almost never	Some-times	Many times	Always
1	did you plan "a escape routes" toward the bathroom in public places?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2	did you feel that you had something that was not well?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3	interfered with your ability to relax in the evening?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4	did you feel frustrated or irritated by the amount of time you spend in the bathroom?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
5	did you avoid activities away from bathrooms (such as walking, jogging, hiking)?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
6	woke you up while you were sleeping ?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
7	did it made you decrease physical activities (exercise, sports, etc. )?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
8	did it caused any problems with your partner or spouse?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
9	did you feel uncomfortable when traveling with other people because you needed to stop to go to the bathroom?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
10	did it influence in yours relationships with family members and friends?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
11	did it made it difficult for the amount of sleep needed?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
12	did you locate the nearest bathroom as soon as you arrived to a place that you had never been before?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>



# COMPLETED BY THE PATIENT

## SHEET 2-3. QUESTIONNAIRE OABq-SF ON OVERACTIVE BLADDER

Researcher Identifier:

Patient Identifier:

### POST-TREATMENT

### SYMPTOMATOLOGY

In this questionnaire you will find questions on how much you have been annoyed about certain symptoms of the bladder during the last 4 weeks. Mark a ✓ or ✗ in the box that best describes how annoying are each symptom during the last 4 weeks. There is no right or wrong answers. Ensure to answer to all the questions.

During the last 4 weeks, how much did you annoy to...?		Nothing	A little	Something	Much	Very Much
1	have wishes to urinate?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
2	have sudden desires to urinate with little or no notice?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
3	have accidental loss of small amounts of urine?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
4	have to urinate at night?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
5	wake up in the night because you had to urinate?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5
6	have loss of urine associated with a strong desire to urinate?	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5

# COMPLETED BY THE PATIENT

## SHEET 2-4. QUESTIONNAIRE OABq-SF ON OVERACTIVE BLADDER

Researcher Identifier:

Patient Identifier:

### POST-TREATMENT

#### LIFE QUALITY

In the following questions, think about the general symptoms of your bladder during the last 4 weeks and the impact they have had on his life. Answer each question as best as possible indicating the frequency with which you have felt it. Mark a ✓ or ✗ in the box that best respond to each question. Ensure to answer to all the questions.

During the last 4 weeks, how often your bladder symptoms...		Never	Almost never	Some-times	Many times	Always
1	did you plan "escape routes" toward the bathroom in public places?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2	did you feel that you had something that was not well?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3	interfered with your ability to relax in the evening?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4	did you feel frustrated or irritated by the amount of time you spend in the bathroom?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
5	did you avoid activities that were away from bathrooms (such as walking, jogging, hiking)?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
6	woke you up while you were sleeping?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
7	did it made a decrease in physical activities (exercise, sports, etc. )?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
8	did it caused any problems with your partner or spouse?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
9	did you feel uncomfortable when traveling with other people because you needed to stop to go to the bathroom?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
10	did it influence in yours relationships with family members and friends?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
11	did it made it difficult for the amount of sleep needed?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
12	did you locate the nearest bathroom as soon as you arrived to a place that you had never been before?	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

SHEET 3. SUMMARY SHEET.

Researcher Identifier:

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Patient Identifier:

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	Pre-treatment	Post-treatment
Score OABq-SF		
Micturition frequency 24 h		
Nocturnal micturition frequency		
Episodes of urgency		
Number of losses/day		
Number of pad/day		

SIDE EFFECTS

# NOTEBOOK DATA COLLECTION STUDY:

|| Effectiveness and tolerability of Contrurine Plus in the treatment of  
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## Authors.

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## RESULTS OBTAINED of the study:

### Efficacy and tolerability of Contrurine Plus in the treatment of overactive bladder in women

#### OBJECTIVES

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Evaluate the efficacy and safety of the drug Contrurine Plus about symptoms and life quality to be coped with urinary incontinence in a cohort of female patients, diagnosed with overactive bladder syndrome.

#### MATERIAL AND METHODS

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36 patients participated in the study with a diagnosis of overactive bladder.

The study was approved by the local ethical committee and informed consent was obtained by writing from all participants in the study.

All of them were administered with the drug Contrurine Plus at a dose of 300 mg daily, for 3 months.

Prior to the treatment, there were recorded variables such as age, sex, weight, height, body mass index [BMI = weight (kg) /height (m)<sup>2</sup>], concomitant medication, medical treatment, prior pelvic prolapse, as well as relevant surgical background, and start and end dates of treatment with the studied drug. It was also identified patients who stopped treatment and the reason being.

We conducted two visits (before treatment start and at the end, 3 months later). In these visits it was supplied the following documentation (for completion by the patient):

- OABq-SF (Annex II) validated for the evaluation of the symptoms and life quality of patients with overactive bladder.

Also in both visits the urologist responsible for patient registered, by means of clinical history:

- Micturition frequency 24 h.
- Nocturnal micturition frequency (nocturia).
- Episodes of urgency.
- Number of losses / day.
- Number of compresses / day.

The improvement was analysed in all the studied parameters in the visit of completion of treatment with respect to the initial visit. The Kolmogorov-Smirnov test was used to check the adjustment of numeric variables to a normal distribution (Gaussian).

We assessed the score in the above questionnaire, before and after treatment.

- OABq –SF. There were analysed separately the scores of paragraph symptomatology (sheet 2-3, sum of the 6 questions), and the life quality (sheet 2-2, sum of the 12 questions). We also analysed the total score of the questionnaire (sum of the score in the two paragraphs above).

Established three categories of effectiveness (improvement, without changes, and worsening), calculating the proportion of patients experiencing improvement in each paragraph. Additionally, we quantified the extent of such improvement (difference between the final score and the initial).

The calculation of the level of statistical significance of the proportion of patients who experienced improvement after the treatment was carried out using the test Chi-square. In terms of the level of significance of the difference scores before and after the treatment it was carried out by Student's t test for paired samples in numeric variables that were adjusted to a normal distribution, and through the range test with sign by Wilcoxon for non-parametric numeric variables.

For the collection of data it was created a database with Microsoft Access. The analysis was conducted with the application SPSS v17.0 for Windows.

The statistical significance level was set at  $p < 0.05$ .

## RESULTS

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### Descriptive statistics

The study included 36 female patients. However, 3 patients were excluded by present acute infection of the urinary tract (acute cystitis) during the study and 1 by withdrawal of treatment without filling in the questionnaire of the study.

Age was found between 35 and 90 years, median 67.5 years, average 62.6, standard error of the mean 2.81.

2 Patients were treated previously with anticholinergics, and 4 were subjected to some surgical procedure of correction of stress incontinence, or prolapsed of the pelvic floor.

BMI was calculated in 27 patients from whom the variables weight and height were simultaneously registered. According to these parameters, 17 patients (63.0 % of the evaluable) presented a normal weight, 9 (33.3 %) were overweight, and 1 (3.7 %) had mild obesity.

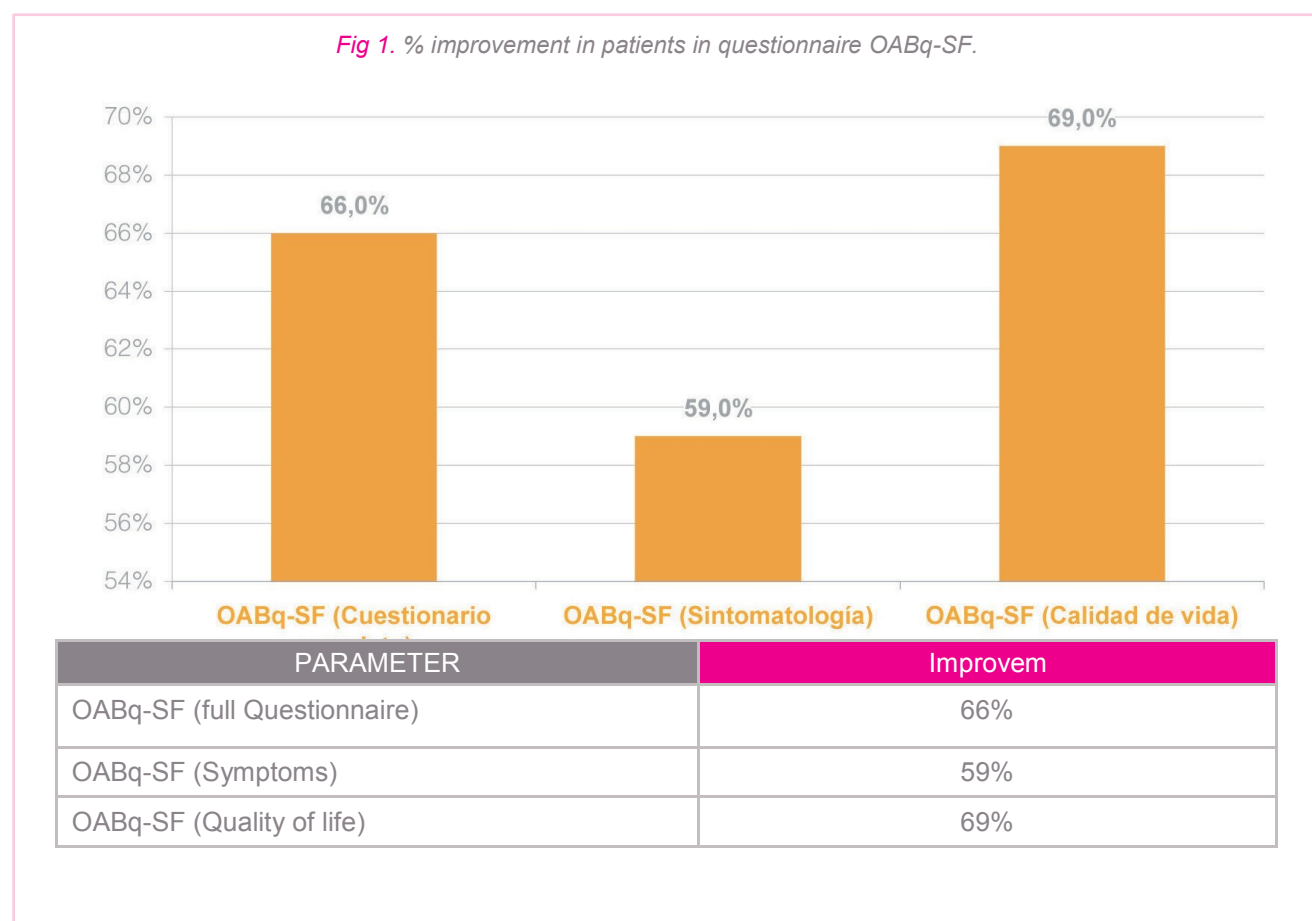


## Effectiveness

In regard to the measures of effectiveness of the treatment, the variables studied (scores in questionnaire OABq-SF) were adjusted to a normal distribution. The variables of effectiveness that were not adjusted to normal were:

- Nocturnal micturition frequency (nocturia), before and after treatment.
- Number of losses before and after treatment.
- Number of compresses used before and after treatment and the difference between the two.

We found a significant improvement in the questionnaire used (OABq-SF). Such improvement was 65.6 % in the OABq-SF ( $p=0.001$ ). The magnitude of this improvement was significant. The average difference quantified was 1.6 in the total score of the OABq-SF. **(Figure 1) (Table 1).**

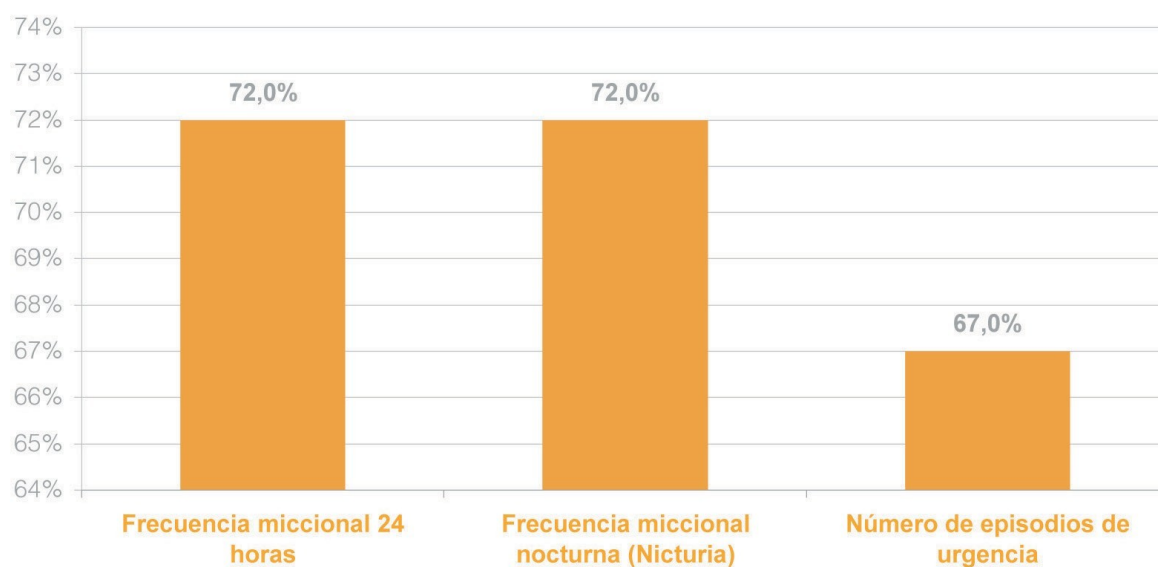


As for the rest of the clinical histories, they also found an improvement in urinary frequency 24 hours, at night (nocturia), number of urgency episodes per day, number of daily losses and number of compresses used. **(Figures 2 and 3).**

**Table 1 . Global data improvement**

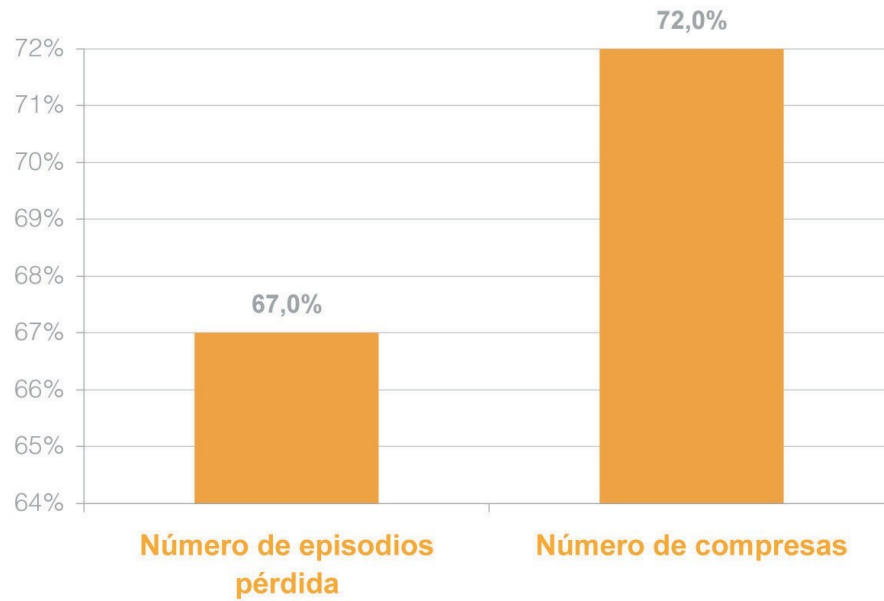
	Mean	Std. Error Of Mean	Mediate	Minimum	Maximum	GIS. (2-tailed)	Test
IMPROVEMENT OABq - SF, FULL QUESTIONNAIRE	<b>1.56</b>	0.148	1.00	1	3	,000	Paired t-test
IMPROVEMENT OABq-SF, SECTION SYMPTOMS	<b>1.63</b>	0.147	1.00	1	3	,000	Paired t-test
IMPROVEMENT OABq-SF SECTION LIFE QUALITY	<b>1.50</b>	0.142	1.00	1	<b>3</b>	,001	Paired t-test
MICTURITION FREQUENCY DIFFERENCE 24 HOURS	<b>2.17</b>	0.422	2.00	0	6	,000	Paired t-test
NOCTURNAL MICTURITION FREQUENCY DIFFERENCE (nocturia)	1.11	0.196	<b>1.00</b>	0	2	,001	Wilcoxon
DIFFERENCE EPISODES URGENCY	<b>1.11</b>	0.241	1.00	0	3	,000	Paired t-test
DIFFERENCE NUMBER LOSSES	1.00	0.214	<b>1.00</b>	0	3	,002	Wilcoxon
DIFFERENCE COMPRESSES NUMBER	0.78	0.129	<b>1.00</b>	0	2	,000	Wilcoxon

*Fig 2. % of patients with improvement symptoms of bladder filling.*



PARAMETER	Improvem
Voiding Frequency 24 hours	72%
Nocturnal micturition frequency (nocturia)	72%
Number of episodes of urgency	67%

**Fig 3.** % patients improvement in incontinence episodes and compresses 24 hours.



PARAMETER	Improvement
Number of episodes loss	67%
Number of compresses	72%

Four patients had grade III cystocele. The treatment was ineffective in all of them (no changes in the scores of the questionnaire or the severity of the symptoms). (Table 2).

**Table 2 . Patients with cystocele III**

	evaluable patients (N)	Improvement
OABq-SF (Full Questionnaire)	4	0 (0 %)
OABq-SF (Symptoms)	4	0 (0 %)
OABq-SF (Quality of life)	4	0 (0 %)
Micturation Frequency 24 Hours	4	0 (0 %)
Nocturnal micturition frequency (nocturia)	4	0 (0 %)
Number of episodes of urgency	4	0 (0 %)
Number of episodes loss	4	0 (0 %)
Number of compresses	4	0 (0 %)

There were excluded from the analysis three patients who had symptoms consistent with acute urinary tract infection (cystitis) during the study. In none of them the treatment had an improvement in the parameters studied (with the solitary exception of micturition frequency 24 hours in one of them). (Table 3).

**Table 3 . Patients with acute cystitis during the study**

	evaluable patients (N)	Improve
OABq-SF (full Questionnaire)	3	0 (0 %)
OABq-SF (Symptoms)	3	0 (0 %)
OABq-SF (Quality of life)	3	0 (0 %)
Micturition Frequency 24 Hours	3	1 (33.3%)
Nocturnal micturition frequency (nocturia)	3	0 (0 %)
Number of episodes of urgency	3	0 (0 %)
Number of episodes loss	3	0 (0 %)
Number of compresses	3	0 (0 %)

## Tolerability

Only adverse effects were observed in one patient (micturition difficulty). There were no dropouts from treatment due to side effects.

## CONSIDERATIONS

Contrurine Plus has demonstrated its effectiveness in overactive bladder cases and nocturia in women.

However, in overactive bladder cases associated with cystocele of high grade (grade III), it was not demonstrated this efficiency, possibly in relation to the existence of obstruction of lower urinary tract (produced by the pelvic prolapse) causing the bladder hyperactivity (*Salinas et al*).

As well as proantocyanidins (PAC's) have shown to be useful in the prevention of recurrent urinary tract infections in women (*Sánchez Ballester et al*), it should be noted that the presentation of episodes of acute urinary tract infection (acute cystitis) in overactive bladder cases in women, would prevent the therapeutic action of Contrurine Plus, demonstrating the ineffectiveness, not as an isolated antibiotic treatment. The usage of PAC's, in the acute episodes of urinary tract infection (as proposed by *Vicariotto et al.*) it should be used, in these cases, the corresponding antibiotic treatment.

The tolerability of Contrurine Plus was good, with mild side effects and reversible.

## REFERENCES

1. Salinas J et al. Urodynamic testing autoreduction of cystocele in the diagnosis of lower urinary tract obstruction. Arch. Esp. Urol. 2007, 60, (9): 1.085 – 1.089.
2. Sanchez Ballester F, Ruiz Vidal V, Lopez Alcina E et al. Cysticlean® a highly standardized content in the prevention of recurrent urinary tract infections: an observational, prospective cohort study. BMC Urol. 2013; 13:28
3. Vicariotto F. Effectiveness of an association of to dry cranberry extract, D-mannose, and the two microorganisms *Lactobacillus plantarum* LP01 and *Lactobacillus paracasei* LPC09 in women affected by cystitis a pilot study. J Clin Gastroenterol. 2014 Nov; 48 Suppl. 1: S96-101.