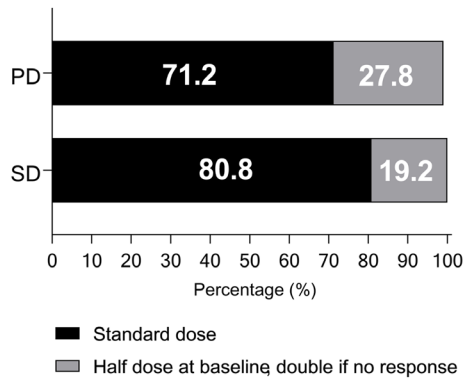
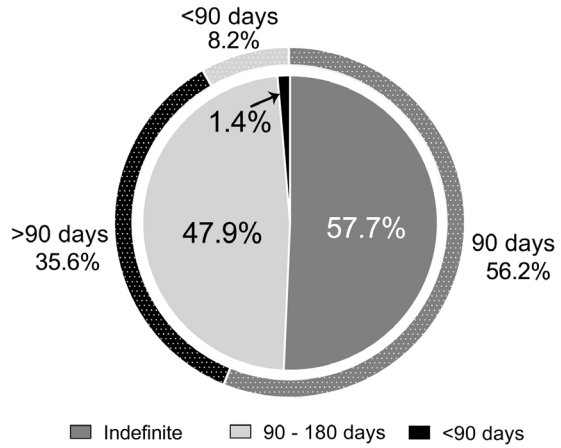


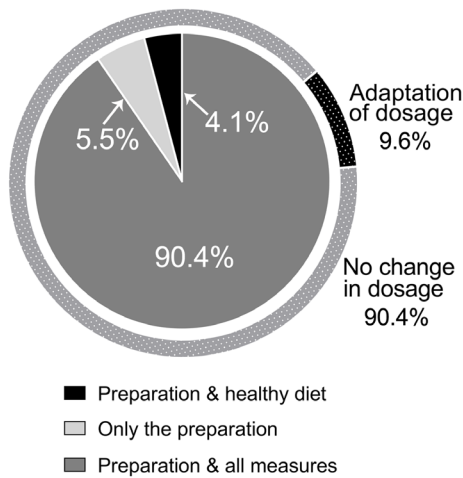
**A INITIAL POSOLOGY ACCORDING TO THE TYPE OF DYSMENORRHEA**



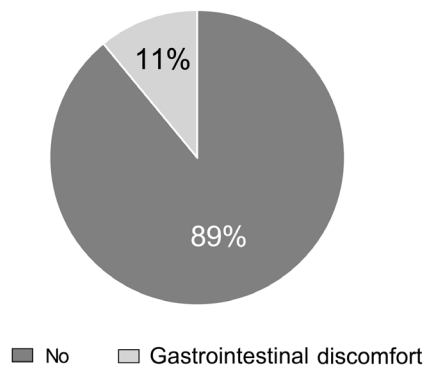
**B TREATMENT DURATION AND FREQUENCY OF EVALUATIONS**



**C HYGIENE AND DIETARY MEASURES AND POSOLOGY ADAPTATION**



**D ADVERSE EFFECTS**



**Supplementary Figure:** A) Initial dosage for Primary Dysmenorrhea (PD) and Secondary Dysmenorrhea (SD), considering NAC 600 mg/day; LA 200 mg/day; Br 25 mg/day; Zn 10 mg/day as standard dose. Initial posology recommendation for PD and SD. (B, inner chart) Duration of NAC/LA/Br/Zn treatment; (B, outer ring) frequency of evaluations. (C, inner chart) Hygiene and dietary measure recommendations and their association with the preparation (Preparation and all measures (healthy diet, regular exercise and avoiding stress) 90.4%; only the preparation 5.5%; Preparation and healthy diet 4.1%); (C, outer ring) Expert adaptation of the preparation posology regarding the hygiene and dietary measure recommendations (No change in dosage 90.4%; Adaptation of dosage 9.6%). D) Adverse effects reported by the patients (89% No; 11% gastrointestinal discomfort). All results are represented as percentage, N=73

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## APPENDIX: STUDY'S SURVEY

### Purpose of the survey

The main objective of the following survey is to know the recommended posology of the prepared composed by N-Acetyl Cysteine (NAC), alpha Lipoic Acid (LA), Bromelain (Br) and Zinc (Zn), (NAC/LA/Br/Zn) in patients presenting dysmenorrhea. NAC/LA/Br/Zn is indicated to relieve chronic pelvic pain associated with endometriosis, with a triple action: antioxidant, anti-inflammatory and analgesic.

Dysmenorrhea is defined as uterine pain that takes place at the time of menstruation. It can occur during menstruations or 1 to 3 days before it begins. The pain tends to be more intense 24 hours after the onset of menstruation and continues for 2 to 3 days. Primary dysmenorrhea is defined as pain during menstruation in the absence of an identifiable origin, while secondary dysmenorrhea is often associated with endometriosis or pelvic anatomical abnormalities.

The survey aims to review the possible treatment guidelines depending on the characteristics of the patients, the degree of pain they experience, as well as the adaptation of the posology during the treatment depend on the evolution of the patients. The secondary objective is to know the recommended dosage of the product regarding the type of dysmenorrhea (primary or secondary) and other causes of pain, together with the evaluation of the patient's satisfaction with the recommended therapeutic regimen.

### Survey

The survey consists of 38 questions divided into 5 blocks of questions that could be multiple-choice or single-choice answer. In many questions you can write your own answer if you do not agree with the options given. The estimated time required to complete the questionnaire is less than 15 minutes.

### BLOCK 1: PRELIMINARY CONSIDERATIONS

1. For which indication do you recommend the prepared NAC/LA/Br/Zn most frequently? (Multiple-choice)
  - a. Primary dysmenorrhea
  - b. Secondary dysmenorrhea
  - c. Other causes of pelvic pain
  - d. Other
2. What is the main reason for recommending the prepared NAC/LA/Br/Zn? (multiple-choice)
  - a. Antioxidant
  - b. Anti-inflammatory
  - c. Analgesic
  - d. Contributes to DNA synthesis
  - e. The combination of all of them
3. What are the general characteristics of the patients to whom you recommend the prepared NAC/LA/Br/Zn? (multiple-choice)
  - a. Woman in pain who doesn't want to take birth control pills
  - b. Woman in pain taking birth control pills
  - c. Woman in pain who is looking for a pregnancy

- d. Sterile woman with pain
- e. Woman who prefers not to take NSAIDs/analgesics
- f. Other

### BLOCK 2: PRIMARY DYSMENORRHEA

4. Before recommending the prepared NAC/LA/Br/Zn, do you assess the type of dysmenorrhea? (Single-choice)
  - a. Yes, always
  - b. Whenever I can
  - c. No
  - d. Other
5. How do you evaluate primary dysmenorrhea? (multiple-choice)
  - a. Interrogation or anamnesis
  - b. Physical exam
  - c. Imaging tests
  - d. Other
6. How do you assess the degree of pain in patients? (multiple-choice)
  - a. Visual Analog Scale (VAS, scale 1-10)
  - b. Numerical Pain Scale (NRS)
  - c. According to the testimony of the patients (mild, moderate, severe).
  - d. Other
7. What is the pain experienced by patients for whom you recommend NAC/LA/Br/Zn? (Single-choice)
  - a. Mild pain, VAS <4
  - b. Moderate pain, VAS 4-7
  - c. Severe pain, VAS >7
  - d. I recommend it for any of the above cases
8. Depending on the pain that patients experience, do you adapt the dosage of NAC/LA/Br/Zn? (Single-choice)
  - a. Yes
  - b. No
9. At the beginning of treatment with NAC/LA/Br/Zn, which concentration do you usually recommend as treatment for primary dysmenorrhea? (Single-choice)
  - a. NAC 300 mg/day, LA 100 mg/day, Br 12.5 mg/day Zn 5 mg/day
  - b. NAC 600 mg/day, LA 200 mg/day, Br 25 mg/day Zn 10 mg/day
  - c. NAC 300 mg/day, LA 100 mg/day, Br 12.5 mg/day Zn 5 mg/day and, in case the patient doesn't respond, I double the concentrations per day.
  - d. Other
10. When a patient is treated first with NAC/LA/Br/Zn, what is your recommendation at the beginning of treatment for primary dysmenorrhea? (Single-choice)
  - a. 3 months of continuous treatment and re-evaluation.

- b. I recommend a long-term regimen, longer than 3 months.
- c. I recommend a short-duration regimen, less than 3 months.
- d. Other

11. If you initially recommend NAC/LA/Br/Zn with a long-term regimen, what regimen do you recommend for primary dysmenorrhea? (Single-choice)

- a. >3 months with 10-day breaks.
- b. >3 months without breaks.
- c. I recommend shorter time therapy at the beginning.
- d. Other

12. If you initially recommend NAC/LA/Br/Zn with a short-duration regimen, what regimen do you recommend for primary dysmenorrhea? (Single-choice)

- a. 5 days prior to menstruation.
- b. 7-15 days prior to menstruation.
- c. 5 days prior to menstruation and 5 days after menstruation.
- d. I do not usually recommend short-term treatment at the beginning.
- e. Other

13. Of the following options, which dosage do you recommend for patients with primary dysmenorrhea with mild pain (<4)? (Single-choice)

- a. 3 months continuous therapy with 10-day breaks.
- b. 3 months continuous therapy and change to 5 days before menstruation, (discontinuous therapy).
- c. 3 months continuous therapy and change to 7-15 days before menstruation (discontinuous therapy).
- d. 5 days before and 5 days after menstruation (discontinuous therapy).
- e. 7-15 days before menstruation (discontinuous therapy).
- f. Other

14. Of the following options, which dosage do you recommend for patients with primary dysmenorrhea with moderate pain (4-7)? (Single-choice)

- a. 3 months continuous therapy with 10-day breaks.
- b. 3 months continuous therapy and change to 5 days before menstruation, (discontinuous therapy).
- c. 3 months continuous therapy and change to 7-15 days before menstruation (discontinuous therapy).
- d. 5 days before and 5 days after menstruation (discontinuous therapy).
- e. 7-15 days before menstruation (discontinuous therapy).
- f. Other

15. Of the following options, which dosage do you recommend for patients with primary dysmenorrhea with severe pain (>7)? (Single-choice)

- a. 3 months continuous therapy with 10-day breaks.

b. 3 months continuous therapy and change to 5 days before menstruation, (discontinuous therapy).

c. 3 months continuous therapy and change to 7-15 days before menstruation (discontinuous therapy).

d. 5 days before and 5 days after menstruation (discontinuous therapy).

e. 7-15 days before menstruation (discontinuous therapy).

f. Other

16. In case you adapt the dosage because the response to treatment, what do you recommend? (Single-choice)

a. From continuous to discontinuous treatment, with treatment taken in the 5 days before menstruation.

b. From continuous to discontinuous treatment, with treatment taken in the 7-15 days before menstruation.

c. From continuous to discontinuous treatment, with treatment taken in the 5 days before and after menstruation.

d. From discontinuous to continuous treatment

e. Other

17. What do you think should be the total duration of treatment with NAC/LA/Br/Zn for patients with primary dysmenorrhea? (Single-choice)

- a. Indefinite
- b. Between 3 and 6 months
- c. <3 months
- d. Other

18. What do you consider to be the time needed to evaluate the effectiveness of NAC/LA/Br/Zn? (Single-choice)

- a. 15 days
- b. 30 days
- c. 90 days
- d. >90 days
- e. Other

19. Do you recommend NAC/LA/Br/Zn in combination with hygienic-dietary measures for patients with dysmenorrhea? (Single-choice)

- a. No, only NAC/LA/Br/Zn
- b. NAC/LA/Br/Zn + regular physical exercise
- c. NAC/LA/Br/Zn + healthy diet
- d. NAC/LA/Br/Zn + avoid stress
- e. NAC/LA/Br/Zn + all measures mentioned above

20. If you recommend hygienic-dietary measures, do you adapt the recommended NAC/LA/Br/Zn regimen? (Single-choice)

- a. I do not change the dosage
- b. Yes, I change the dosage. Please indicate which one

### BLOCK 3: SECONDARY DYSMENORRHEA AND

## OTHER CAUSES OF PAIN

21. At the beginning of treatment with NAC/LA/Br/Zn, which concentration do you usually recommend as treatment for secondary dysmenorrhea associated with endometriosis? (Single-choice)

- a. NAC 300 mg/day, LA 100 mg/day, Br 12.5 mg/day Zn 5 mg/day
- b. NAC 600 mg/day, LA 200 mg/day, Br 25 mg/day Zn 10 mg/day
- c. NAC 300 mg/day, LA 100 mg/day, Br 12.5 mg/day Zn 5 mg/day and in case the patient doesn't respond, I double the concentrations per day.
- d. Other

22. When a patient is treated first with NAC/LA/Br/Zn, what is the recommended duration of treatment for secondary dysmenorrhea associated with endometriosis? (Single-choice)

- a. <3 months
- b. 3 months
- c. >3 months with 10-day breaks.
- d. >3 months without breaks.
- e. Other

23. For patients with endometriosis-associated secondary dysmenorrhea with mild pain (<4), which dosage do you recommend? (Single-choice)

- a. 3 months continuous therapy with 10-day breaks.
- b. 3 months continuous therapy and change to 5 days before menstruation, (discontinuous therapy).
- c. 3 months continuous therapy and change to 7-15 days before menstruation (discontinuous therapy).
- d. 5 days before and 5 days after menstruation (discontinuous therapy).
- e. 7-15 days before menstruation (discontinuous therapy).
- f. Other

24. For patients with endometriosis-associated secondary dysmenorrhea with moderate pain (4-7), which dosage do you recommend? (Single-choice)

- a. 3 months continuous therapy with 10-day breaks.
- b. 3 months continuous therapy and change to 5 days before menstruation, (discontinuous therapy).
- c. 3 months continuous therapy and change to 7-15 days before menstruation (discontinuous therapy).
- d. 5 days before and 5 days after menstruation (discontinuous therapy).
- e. 7-15 days before menstruation (discontinuous therapy).
- f. Other

25. For patients with endometriosis-associated secondary dysmenorrhea with severe pain (>7), which dosage do you recommend? (Single-choice)

- a. 3 months continuous therapy with 10-day breaks.
- b. 3 months continuous therapy and change to 5 days before

menstruation, (discontinuous therapy).

- c. 3 months continuous therapy and change to 7-15 days before menstruation (discontinuous therapy).
- d. 5 days before and 5 days after menstruation (discontinuous therapy).
- e. 7-15 days before menstruation (discontinuous therapy).
- f. Other

26. When the patient presents dysmenorrhea associated with other pathologies (e.g., chronic pelvic pain, myoma), do you recommend NAC/LA/Br/Zn as a treatment? (Single-choice)

- a. Yes
- b. No, only for endometriosis and/or dysmenorrhea associated with endometriosis
- c. Other

27. If you recommend NAC/LA/Br/Zn to a patient with dysmenorrhea associated with other pathologies, what dosage do you usually recommend? (Single-choice and NOT mandatory)

- a. 3 months continuous therapy with 10-day breaks.
- b. 3 months continuous therapy and change to 5 days before menstruation, (discontinuous therapy).
- c. 3 months continuous therapy and change to 7-15 days before menstruation (discontinuous therapy).
- d. 5 days before and 5 days after menstruation (discontinuous therapy).
- e. 7-15 days before menstruation (discontinuous therapy).
- f. Other

## BLOCK 4: ASSOCIATIONS WITH OTHER DRUGS

28. In patients treated with non-steroidal anti-inflammatory drugs (NSAIDs), what dosage of NAC/LA/Br/Zn do you recommend? (Single-choice)

- a. I do not recommend NAC/LA/Br/Zn
- b. I do not modify the dosage
- c. I recommend reducing the concentration of NAC/LA/Br/Zn
- d. Other dosage. Please indicate the dosage

29. In patients treated with combined hormonal contraception, what dosage of NAC/LA/Br/Zn do you recommend? (Single-choice)

- a. I do not recommend NAC/LA/Br/Zn
- b. I do not modify the dosage
- c. I recommend reducing the concentration of NAC/LA/Br/Zn
- d. Other dosage. Please indicate the dosage

30. In patients treated with gestagens (norethisterone, Dienogest, IUD), what dosage of NAC/LA/Br/Zn do you recommend? (Single-choice)

- a. I do not recommend NAC/LA/Br/Zn
- b. I do not modify the dosage

c. I recommend reducing the concentration of NAC/LA/Br/Zn

d. Other dosage. Please indicate the dosage

31. In patients treated with hypoglycemic drugs, what dosage of NAC/LA/Br/Zn do you recommend? (Single-choice)

a. I do not recommend NAC/LA/Br/Zn

b. I do not modify the dosage

c. I recommend reducing the concentration of NAC/LA/Br/Zn

d. Other dosage. Please indicate the dosage

## BLOCK 5: PATIENT SATISFACTION

32. How often do you usually do a follow up of patients with dysmenorrhea

to whom you have recommended NAC/LA/Br/Zn? (Single-choice)

a. Once or twice a month

b. Once every three months

c. Once every six months

d. Other

33. According to the feedback of your patients treated with NAC/LA/Br/Zn, do you adapt or modify the dosage? (Single-choice)

a. Yes

b. No

c. Other reasons

34. If you adapt the treatment regimen, what dosage do you usually change to? (Single-choice)

a. To continuous treatments (>3 months).

b. To discontinuous treatments 5 days prior to menstruation.

c. To discontinuous treatments 7-15 days prior to menstruation.

d. To discontinuous treatments 5 days before and after menstruation.

e. Other

35. Have any patients reported ineffectiveness after the first 15 days of treatment with NAC/LA/Br/Zn (Single-choice)?

a. Yes

b. No

36. Has any patient reported any adverse reaction during treatment with NAC/LA/Br/Zn? (Single-choice)

a. Yes

b. No

37. If any patient reported any adverse reaction, could you please indicate which one? (Short answer)

38. If you have any suggestions or comments, please feel free to express them in the box below.