



Pharmacoeconomics of Cyclamen europaeum in the management of Acute Rhinosinusitis

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Complete List of Authors:	Mullol, Joaquim; Hospital Clínic, IDIBAPS, CIBERES., Rhinology Unit & Smell Clinic, ENT Department. Crespo, Carlos; Universtisty of Barcelona, Statistics; Oblikue Consulting, Health Economics & Outcomes Strategy Carre, Carme; Hartington Pharmaceuticals, Brosa, Max; Oblikue Consulting,
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Review

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3 **Pharmacoeconomics of *Cyclamen europaeum* in the management of**
4 **Acute Rhinosinusitis**
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8 **Running title:** Pharmacoeconomics of *Cyclamen europaeum*
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10
11 Joaquim Mullol ¹

12 Carlos Crespo ^{2,3}

13 Carme Carré ⁴

14 Max Brosa ²
15
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18
19 ¹ Rhinology Unit & Smell Clinic, ENT Department. Hospital Clínic, IDIBAPS,
20 CIBERES. Barcelona, Catalonia. (Spain)

21 ² Oblikue Consulting, Barcelona (Spain)

22 ³ Department of Statistics. University of Barcelona, Barcelona (Spain)

23 ⁴ Hartington Pharmaceuticals, Barcelona (Spain)
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29 **Corresponding author:**
30
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32 Carlos Crespo

33 c/ Josep Irla i Bosch, 5-7 Primera Planta

34 08034-Barcelona (Spain)

35 Phone: +34932521377

36 Fax: +34932051447

37 Email: carlos.crespo@oblikue.com
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ABSTRACT

Objective. To carry out a pharmacoeconomic analysis of *Cyclamen europaeum* (CE) in the management of acute rhinosinusitis (ARS) in Spain using data from the PROSINUS study.

Study Design. This was a prospective observational study to compare the effectiveness and cost-effectiveness between therapies including CE vs. other therapies in the management of ARS.

Methods. The study was carried out as a secondary analysis of the PROSINUS, combining healthcare resource use, productivity losses, and health outcomes from the observational study with costs representative of the Spanish Health System.

Results. CE given as monotherapy appears to be more effective (cure rate) than other monotherapies (15.3% higher, $p < 0.05$) and combination (10.3% higher, $p < 0.05$) therapies. The addition of CE to other single-drug or combination therapies showed a statistically significant improvement in terms of cure rates when adding CE to 2-drug combinations (93.9% vs. 76.5%; $p < 0.05$), and no significant effect when added to combinations of three or more drugs (81.1% vs. 79.8; NS). CE-based therapies generally showed lower indirect costs, although only the comparison of CE alone vs. other monotherapies, with a net cost savings of 101€ per patient, reached statistical significance (331€ vs. 432€, $p < 0.05$). In addition, CE-based therapies show lower cost per cured patient in all comparisons except when CE was used in combination with three or more other drugs.

Conclusions. The use of *Cyclamen europaeum* may be associated to better clinical outcomes at no additional cost for the healthcare system, respect to treatments commonly used for ARS in clinical practice.

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Keywords: Pharmacoeconomics, Cyclamen europaeum, acute rhinosinusitis, costs, effectiveness.

Level of Evidence: 2c

For Peer Review

INTRODUCTION

Rhinosinusitis is an inflammatory process of the paranasal sinuses with high prevalence in clinical practice^{1,2}. Acute rhinosinusitis (ARS) is an inflammatory alteration of the nose and paranasal sinuses. ARS is usually caused by a viral infection, although other processes such as allergic rhinitis, pathological abnormalities, nasal polyps, or nasal decongestant abuse, can constitute predisposing factors. Inflammation in nasal cavity mucosa results in some disorders of the absorption, protection and transport functions, and complications like asthma flare-ups, chronification of ARS, meningitis, vision problems and ear infections. In ARS the most common symptoms experienced by patients are nasal obstruction, mucopurulent rhinorrhoea, and localized frontal or facial pain.

It is currently accepted that ARS is a frequent disease and, therefore, has a considerable impact on general public health and economic resources, both in terms of those allotted to treatment disease as well as those related to patient labor productivity. In the United States, it was estimated that in 1996 the costs that could be attributable to rhinosinusitis reached 3,390 million dollars³. The number of cases in Spain could range between 440,000 and 1,760,000 per year, with a considerable associated cost².

ARS treatment goals should be symptomatic relief, accelerating remission and preventing complications. Indeed, there is a weak body of clinical evidence about treatment effectiveness and controlled clinical trials of ARS therapies are not numerous⁴. Most authors and consensus papers show little evidence on the effectiveness of treatments based on antibiotics⁵, oral steroids⁶, antihistamines,

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3 nasal irrigation, mucolytics and phytotherapy⁷. The treatment recommended for
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5 ARS by the EPOS consensus (*European Position Paper on Rhinosinusitis and*
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7 *Nasal Polyps*)⁷ is based on symptomatic relief (analgesics, saline serum and
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9 decongestants) or on the use of topical nasal steroids and antibiotics for the
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11 specific patients that can respond, depending on the etiology, severity and
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13 evolution of the clinical pattern⁸. Upon analyzing evidence of adjuvant treatment
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15 aimed to relief symptoms, it can be concluded that it is low. In Spain, the
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17 PROSINUS study⁹ a large observational study showed that less than one fourth
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19 (24%) of 2,610 patients with ARS followed EPOS guidelines, and a number of
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21 different treatments and drug combinations were used.
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29 *Cyclamen europaeum* has been used for a very long time, particularly in South-
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31 East Europe, as a traditional treatment for nasopharyngeal diseases. *Cyclamen*
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33 *europaeum* (*CE*) is prepared on the basis of an aqueous extract of tubers of *CE*,
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35 that contain a mixture of saponins, which characteristically causes local osmosis
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37 and stimulation of the ending terminal of the trigemin and increases the secretion
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39 of the nasal mucos^{10, 11}. *CE* has shown its efficacy in two placebo-controlled clinical
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41 trial and 13 head to head studies (9 in adults and 5 in children) that compared *CE*
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43 with other active treatments that seem to indicate that *CE* may contribute to
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45 reducing disease progression time, improving symptoms relief and objective
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47 response (CT-scan), decreasing the need for antibiotics or boosting their effects,
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49 as well as reducing the number of complications and chronification¹².
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58 The present study has analysed data from the PROSINUS study to carry out a
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3 pharmacoeconomic analysis of *CE* in the management of ARS in Spain.
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10 **MATERIALS AND METHODS**

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20 The PROSINUS study included 2,610 patients visited by 287 specialists in
21 otorhinolaryngology throughout Spain. Patients had to fulfil all inclusion criteria:
22 either sex, ≥ 18 years of age, reporting to the otorhinolaryngologist's office with
23 symptoms compatible with the epidemiological diagnosis of ARS according to the
24 EPOS consensus "sudden onset of two or more symptoms, one of which should be
25 either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior
26 nasal drip), \pm facial pain/pressure, \pm reduction or loss of smell; for a duration of < 12
27 weeks". Patients voluntarily gave their consent to take part in this study and they
28 had none of the exclusion criteria: established diagnosis of chronic rhinosinusitis
29 (with or without nasal polyps, and presenting with a new event or acute
30 exacerbation of their disease), concurrent use of medication for other conditions
31 that could interfere with the sinonasal disease, existing social or cognitive features
32 indicating the possibility of problems in the follow-up or a high risk of withdrawing
33 prematurely from the study. Data on the previous management by Primary Care
34 Physicians was also recorded.
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Study design

The PROSINUS study was an epidemiological, observational, prospective, health outcomes study aimed to describe the diagnostic, treatment and clinical monitoring procedures applied in ARS in clinical practice in Spain. Since this was an observational study aimed at identifying current practice real failure rates, and costs associated with usual medical care and not under experimental conditions, treatment of the ARS was left to the criteria of the attending physician. The present study was carried out as a secondary analysis of the PROSINUS database, combining healthcare resource use, productivity losses and health outcomes from the observational study with updated unit costs representative of the Spanish National Health System (SNHS). Data for both clinical and economic variables (see below) were recorded prospectively by the investigators (from symptoms onset until first study visit, and from first study visit to final study visit, 2 to 4 weeks after first visit).

Comparative options

Costs and outcomes of *CE* in monotherapy and combination therapy were compared to both monotherapies and combinations therapies as follows:

- *CE* in monotherapy vs. other pooled monotherapies and vs. combinations of two or more pooled drug combinations without *CE*.

- *CE* added to different combinations, specifically: *CE* added to one single drug, *CE* added to two drug combination, and *CE* added to three or more combined drugs.

Additional analysis was carried out to address the effect of adding *CE* to antibiotics and antibiotics + corticosteroids⁸.

In all cases, comparison options were defined by means of the treatments prescribed by the patients at the first visit of the study, irrespective of treatments taken previously (from event onset to first physician visit).

Clinical outcomes

Cure rate was defined following the EPOS consensus for epidemiological definition⁷ as the complete clinical resolution of ARS symptoms of the ARS episode at the end of the study follow-up (visit 2 at 2-4 weeks) and was calculated for each comparison option. For the primary analysis, the patient sample that met all of the inclusion criteria and none of the exclusion criteria and which had valid data for the primary endpoint was used. No provision was made for interpolating missing data or loss to follow-up.

Economic outcomes

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3 Both direct and indirect costs were included in the analysis. Direct costs included
4 medical visits (general practitioner, otorhinolaryngologist and emergency visits),
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6 diagnostic tests (rhinoscopy or nasal endoscopy, sinus X-ray, sinus CT, bacteria
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8 culture and allergy tests) and drugs (oral antibiotics, nasal corticosteroids,
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10 antihistamines, nasal decongestants, mucolytics, saline solutions, and
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12 phytotherapy including *CE*). Indirect costs included sick leaves (absenteeism) and
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14 reduced productivity at work (presenteeism). In the PROSINUS study, resources
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16 use from the onset of the ARS event to the date of the visit was also recorded at
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18 the first study visit. At the second visit, resources uses from first visit to the end of
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20 the event were recorded. Thus, otorhinolaryngologists could have influence in the
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22 resources use after but not before the first visit since symptoms onset.
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32 Unit costs applied to the health resources utilization data are shown in Table 1.
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34 The data sources were the Medicine Database of the General Council of
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36 Pharmacists Official Colleges (BOTPLUS)¹³ for drug costs, and the Health Costs
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38 Database eSalud¹⁴ for healthcare resources (medical visits and tests). With respect
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40 to the medication, it was assumed that a patient would purchase one pack of each
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42 type of drug that he/she used. All costs were expressed in euros of 2011.
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48 Perspective, time horizon and discount rate
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53 The main analysis was carried out from the societal perspective (including both
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55 direct and indirect costs). Additional analysis adopted the healthcare perspective
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(direct costs only). Since study follow-up was short (1 month) no discounting was applied in the analysis.

Statistical Analysis

Statistical analysis was performed with SPSS version 15.0 for Windows (SPSS Inc., Illinois, USA). ANOVA was carried out to see if there was any difference between subgroups and logistic regression models were built to determine whether specific drugs had a significant influence in the cure rate of pooled options, to discard relevant heterogeneity of comparison options in the analysis.

Student's t-test and CHI-square test were used to compare mean costs and cure rates of CE-based therapies respect to comparators. The level of statistical significance was established at 0.05.

RESULTS

On average, patients reported to the first PROSINUS study visit 11.2 (± 6.2) days after onset of the ARS event, while the average total duration of the event was 13.7 (± 8.8) days. At visit 2, 82.9% of patients presented complete clinical resolution of the symptomatic episode. Table 2 shows the clinical results of the comparison of CE based therapies respect to other therapies in the management of ARS. CE in monotherapy appeared to be more effective in terms of cure rate than other pooled monotherapies (15.3% higher, $p < 0.05$) and combination therapies (10.3% higher, $p < 0.05$). The addition of CE to other monotherapies or combination therapies

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3 showed a significant improvement when adding *CE* to 2-drug combinations (93.9%
4 vs. 76.5%; $p < 0.05$), but no significant effect when added to combinations of three
5 or more drugs (81.1% vs. 79.8%; NS).
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12 Patients receiving *CE* monotherapy were 98€ less costly than patients receiving
13 other monotherapies (682€ vs. 584€, $p < 0.05$) and 61€ less costly than combination
14 therapies (645€ vs. 584€, $p < 0.05$). Figure 1 show the breakdown of these results in
15 terms of direct and indirect costs. *CE* as an add-on treatment was associated to
16 lower total costs when used in combination with one single drug (626€ vs. 682€,
17 $p = 0.29$), even though these differences didn't reach the statistical significance,
18 probably because of the limited sample size. The combination of *CE* with 2 or more
19 drugs produced similar total costs than the same combinations without *CE*. In all
20 situations, cost reductions associated to *CE*-based therapies were mainly
21 explained by indirect costs, whilst direct healthcare costs were similar in all
22 subgroups (see table 3). The proportion of patients treated with *CE* that were
23 visited by PCP or PCP and ORL was slightly higher than for patients not taking *CE*,
24 but differences were only significant vs patients treated with antibiotics (which
25 accounted for a small subgroup of patients). This fact could yield to higher costs for
26 *CE* patients but this is not the case because of the lower number of total visits in
27 this group.
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50 The combination of total costs and cure rates provides an estimate of the balance
51 between cost and outcomes, showing lower cost per cured patient in *CE* based
52 therapies in almost all comparisons (except when added to combinations of 3 or
53 more drugs) (Figure 2).
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Special situations

Since only antibiotics, either in monotherapy or combined with corticosteroids have demonstrated a clinical efficacy in the management of ARS, a specific analysis was carried out to compare these options with and without *CE*. The results of this analysis showed that adding *CE* to one antibiotic, with or without nasal corticosteroid, increased the success rate and reduced total costs, due to a significant reduction of indirect costs. Both compared to antibiotic in monotherapy or to antibiotic plus nasal corticoid, the addition of *CE* resulted in a lower cost per success ratio (table 4).

DISCUSSION

This secondary analysis of the PROSINUS study, an observational, prospective, health outcomes study aimed to describe the management of ARS and its outcomes, has shown that *CE* based therapies are associated to better clinical outcomes with similar or even lower costs than comparable therapies without *CE*.

These results are in line with the conclusions of most of the clinical studies on ARS, including placebo-controlled clinical trials and head to head clinical studies. Pfaar et al., in a randomized controlled trial in patients with moderate-to-severe ARS, demonstrated that *CE* on the top of regular antibiotic treatment added a

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3 significant improvement of facial pain/pressure and signs of nasal inflammation
4 compared to antibiotic alone¹². *CE* is a safe and well tolerated treatment that
5 demonstrated a great reduction in individual symptoms scores (nasal obstruction,
6 mucus secretion, facial pain and loss of smell), an improvement in the mucosal
7 edema and nasal obstruction evaluated by endoscopy and a reduction of the sinus
8 occlusion evaluated by CT-scan on day 7¹⁵. The effects of *CE* on ARS start at 3-5
9 days of treatment and the complete symptom resolution at 9-12 day¹⁵. *CE* was able
10 to reduce the disease progression time, the need for antibiotics or boosting their
11 effects, the number of complications and the disease chronification with a great
12 satisfaction scores rated by patients and investigators compared to antibiotic
13 treatment¹². Several drugs, like antibiotics, oral decongestants, antihistamines, and
14 topical corticosteroids are used for the treatment of RS but these available
15 therapies don't have sufficient evidence to be considered efficacious and often fail
16 to provide adequate symptoms relief and or objective cure assessed by endoscopy
17 or CT-scan. Consequently, patients with ARS are often poorly treated and / or
18 treated using several therapies. Despite continued development of new therapies
19 and more accurate diagnostic procedures, there is no evidence that ARS is being
20 better controlled. *CE* could be considered a recommendable option as a first line
21 treatment as it has demonstrated in several clinical studies its ability improving the
22 signs and symptoms of the disease. Besides, Savvateeva and Lopatin¹⁶ have
23 recently published a review of studies that evaluated the efficacy and safety of *CE*
24 and concluded that it provides a good option for ARS treatment, ensuring
25 personalized treatment and preventing polymedication and inappropriate use of
26 antibiotics.

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6 As ARS frequently occurs in conjunction with asthma, allergic rhinitis, and other
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8 airway disorders, it is difficult to single out the expenditures devoted to treating
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10 rhinosinusitis only, and only a few studies have done so¹⁷ and results are notably
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12 variable. Anzai et al.¹⁸ examined the cost-effectiveness of four treatment strategies,
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14 with and without antibiotics, for adult patients with acute sinusitis, finding a total
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16 cost per patient between \$747 and \$899 in 2005. Bhattacharyya et al.^{19, 20} have
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18 recently published two studies of the burden of rhinosinusitis (recurrent ARS and
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20 chronic rhinosinusitis respectively), with total cost per patient/year of \$1,091 and
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22 \$780. These results are hardly comparable with those from our study, since we
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24 focused in costs associated to a single ARS event, whilst those mentioned studies
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26 analysed longer time horizons. Finally, pharmacoeconomic analysis of two
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28 antibiotic therapies found a direct healthcare cost per ARS episode of \$171-\$211 in
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30 2002²¹, slightly lower than our estimates of 250€-329€.
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39 Given the high prevalence of ARS and the eventual consequences of treatment
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41 failure, including potential disease chronification, clinical success should be
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43 pursued in order not only to improve patients' quality of life but to limiting the
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45 economic impact of the condition.
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48 In our study the use of *CE* was associated to a higher cure rate without increasing
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50 healthcare costs, either when compared as monotherapy respect to other
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52 monotherapies, or when added to different combinations. It is important to note
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54 that not properly treated rhinosinusitis could lead to a recurrence or even to a
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56 potential chronification of the disease whereas consequently reducing patient's
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3 overall well-being and quality of life and increasing direct and indirect costs¹⁹.
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5 Therefore, in this sense cyclamen provides an added value because reduces
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8 chronification of ARS. Besides, cyclamen has a purely physiological effect and is
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10 not absorbed, showing a better safety profile compared to other treatments that
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12 cause more or worse adverse events and consequently produce a greater cost
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14 derived from adverse event management²².
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20 This study has two main limitations that must be considered. First, the use of the
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22 data from an observational descriptive study to derive conclusions regarding the
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24 consequences of different treatment options is risky, i.e., the PROSINUS study
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26 was not designed to compare different therapies, and patients' characteristics may
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28 be assumed equivalent irrespective of treatment received, so a selection bias could
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30 exist. Considering the ethical and logistical weaknesses of randomised clinical
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32 trials, well designed and conducted observational studies may be an efficient
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34 alternative to explore exposure effectiveness, even though comparability
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36 across exposure groups may not be guaranteed. Second, the comparison
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38 options built in the secondary analysis include the outcomes of patients that
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40 received different drugs in different combinations, e.g., the pooled results of *CE* vs.
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42 other monotherapies included a number of different drugs in the group 'other
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44 monotherapies'. However, logistic regression techniques were applied to address
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46 whether this pooling of clinical results were justifiable, i.e., no statistical differences
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48 between individual treatments (or combinations) were stated before aggregating
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50 patients in the pool analysis. These limitations raise the need for further research
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52 to definitely establish the clinical superiority of *Cyclamen* in different clinical
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3 situations and combined with different treatments.
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8 Finally, it is noteworthy that the present study is pragmatic and widely applicable in
9 clinical practice, and although it has the mentioned limitations, especially in relation
10 to the selection of treatments, we can conclude that the trend *Cyclamen*
11 *europaeum* has in monotherapy for ARS is cost efficient. However, further studies
12 are needed with greater control in order to conclude on the effect of cyclamen with
13 other treatment combinations of ARS..
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27 **CONCLUSIONS**

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31 The results of this study suggest that the use of *CE*, both as monotherapy or in
32 combination, may be associated to better clinical outcomes, including cure rate, at
33 no additional cost for the healthcare system, respect to different treatment options
34 commonly used in clinical practice for the treatment of ARS.
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3 **Figure 1.** Results of the cost analysis – CE monotherapy vs other monotherapies
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5 (pooled) and combinations
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10 **Figure 2.** Total cost per cured patient
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12 **Legend:** CE: Cyclamen europaeum
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For Peer Review

Table 1. Unit costs used in the analysis

Item	Cost (€)
Drug Cost (per package)	
Oral antibiotics	16.30
Nasal corticosteroids	14.59
Antihistamines	9.48
Decongestants	4.56
Mucolytics	4.31
Saline solutions	2.20
Phytotherapy (including CE)	26.00
Cost of diagnostic tests (per procedure)	
Sinus X-ray	8.00
Sinus CT	87.60
Bacterial culture	10.50
Allergy tests (per procedure)	64.80
Cost per visit	
Emergency at Primary Care Centre	50.10
Primary care physician	33.40
Otorhinolaryngologist (1 st visit)	103.65
Otorhinolaryngologist (subsequent visit)	44.60
Other specialists	44.60

Sources: BOTPLUS 2011, eSalud 2011. CE: Cyclamen europaeum; CT: computerized tomography

Table 2. Cure rates of *Cyclamen*-based options vs. other treatment options (comparators).

Comparison	Cyclamen % mean (SD)	Comparator % mean (SD)	Difference %	p-value
<i>Cyclamen</i> monotherapy (n=90) vs. Other monotherapies (pooled) (n=68)	88.8 (31.8)	73.5 (44.4)	+15.3	<0.05
<i>Cyclamen</i> monotherapy (n=90) vs. Other combinations (pooled) (n=221)	88.8 (31.8)	78.5 (41.1)	+10.3	<0.05
<i>Cyclamen</i> (n=61) + 1 drug (pooled) vs. 1 single drug (pooled) (n=68)	81.7 (39.0)	73.5 (44.4)	+8.2	NS
<i>Cyclamen</i> (n=82) + 2 drugs combinations (pooled) vs. 2 drugs combinations (pooled) (n=87)	93.9 (24.1)	76.5 (42.7)	+17.4	<0.05
<i>Cyclamen</i> + 3 or more drug combinations (pooled) (n=86) vs. 3 or more drug combinations (pooled) (n=134)	81.1 (40.0)	79.8 (39.0)	+1.3	NS

NS: non-significant; SD: standard deviation

Table 3. Results of the cost analysis. CE in combination

	1 single drug (n=68)	<i>Cyclamen</i> + 1 drug (n=61)	Difference	p-value
Total costs, mean (SD)	682 € (233 €)	626 € (359 €)	-56 €	NS
Direct	250 € (135 €)	269 € (108 €)	+19 €	NS
Indirect	432 € (193 €)	357 € (328 €)	-75 €	NS
	2 drugs (n=87)	<i>Cyclamen</i> + 2 drugs (n=82)	Difference	p-value
Total costs, mean (SD)	628 € (235 €)	629 € (245 €)	+1 €	NS
Direct Costs	258 € (SD 107 €)	290 € (SD 89 €)	+32 €	NS
Indirect Costs	370 € (SD 205 €)	339 € (SD 209 €)	-31 €	NS
	3 or more drugs (n=134)	<i>Cyclamen</i> + 3 or more drugs (n=86)	Difference	p-value
Total costs, mean (SD)	656 € (1089 €)	691 € (263 €)	+34 €	NS
Direct Costs	278 € (182 €)	329 € (464 €)	+50 €	NS
Indirect Costs	378 € (616 €)	362 € (367 €)	-16 €	NS

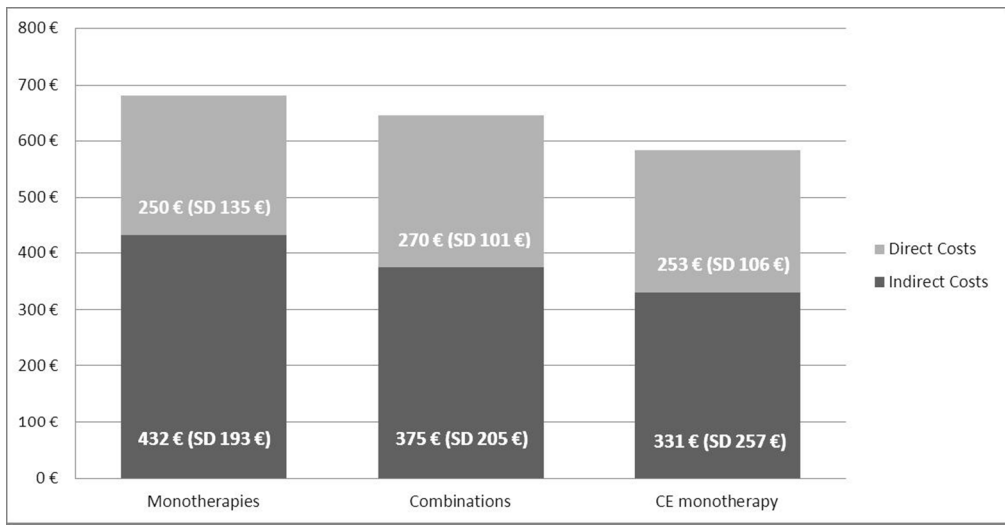
NS: non-significant; SD: standard deviation

Table 4. Costs and outcomes of adding CE to antibiotic with or without corticosteroids

	Antibiotic (n=14)	CE + Antibiotic (n=24)	Difference	p-value
Total costs, mean (SD)	686 € (233 €)	479 € (261 €)	-206 €	<0.05
Direct	247 € (97 €)	255 € (117 €)	+8 €	NS
Indirect	439 € (201 €)	224 € (223 €)	-214 €	<0.05
Cure rate, mean (SD)	60.0% (50.7)	91.3% (28.8)	+31.3%	NS
Cost per cured patient	1.143 €	525 €		
	Antibiotic + Corticosteroid (n=14)	CE + Antibiotic + Corticosteroid (n=19)	Difference	p-value
Total costs, mean (SD)	648 € (194 €)	650 € (182 €)	+2 €	NS
Direct	292 € (95 €)	292 € (57 €)	0 €	NS
Indirect	355 € (356 €)	358 € (187 €)	-2 €	NS
Cure rate, mean (SD)	57.0% (51.0)	100% (0)		
Cost per cured patient	1.134 € (816 €)	650 € (182 €)		

NS: non-significant; SD: standard deviation.

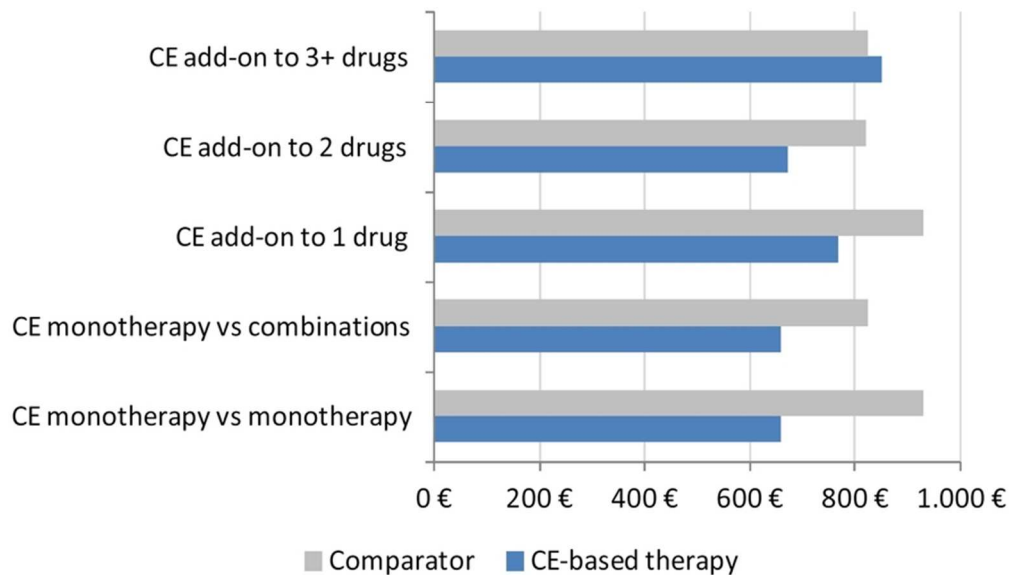
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Results of the cost analysis – CE monotherapy vs other monotherapies (pooled) and combinations. 195x101mm (150 x 150 DPI)

Peer Review

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Total cost per cured patient/CE: Cyclamen europaeum
74x43mm (300 x 300 DPI)