



Contents lists available at ScienceDirect

# European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: [www.elsevier.com/locate/ejogrb](http://www.elsevier.com/locate/ejogrb)

Full length article

## Ulipristal acetate for pre-operative management of uterine fibroids: Modeling outcomes and costs

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## ARTICLE INFO

*Article history:*

Received 21 August 2017

Received in revised form 8 January 2018

Accepted 16 January 2018

Available online xxx

*Keywords:*

Costs and cost analysis

Economic model

Leiomyoma

Markov chains

Quality-adjusted life years

## ABSTRACT

**Objectives:** The aim of this study was to evaluate the pharmacoeconomic profile in Italy of preoperative treatment with ulipristal acetate at the dose of 5 mg/day for 13 weeks in comparison with placebo prior to surgical management of symptomatic uterine fibroids.

**Study design:** The pharmacoeconomic analysis was based on the calculation of incremental cost-effectiveness ratio (ICER). Effectiveness data were derived from the randomized-controlled trial PEARL-1, whilst costs data were retrieved from the published literature. A Markov model was employed to simulate the pattern of costs and two univariate sensitivity analyses tested the robustness of the results.

**Results:** In comparison with placebo, ulipristal acetate 5 mg for presurgical therapy was estimated to be associated with an incremental cost of €351 per patient. Costs per patient were €3836 for ulipristal acetate vs €3485 for placebo. The incremental effectiveness was 0.01931 QALYs per patient (around 7 quality-adjusted days per patient). Hence, the cost effectiveness ratio was calculated to be €18,177 per QALY gained.

**Conclusions:** Preoperative use of ulipristal acetate 5 mg in patients with uterine fibroids has a favourable pharmacoeconomic profile.

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### Introduction

In women in reproductive age, uterine leiomyomas (or fibroids) may cause several symptoms including excessive bleeding, pelvic pain, iron deficiency anemia, infertility and reduced quality of life. Apart from surgical intervention, there are no medical treatments that completely eliminate fibroids. However, medical treatments (e.g. GnRH analogues, oral progestogens and the levonorgestrel intrauterine system) can effectively be employed in the pre-operative period for the reduction of symptoms, in particular heavy bleeding and anemia.

Results of a pivotal randomized controlled trial (the PEARL-I study [1]) have shown that treatment with ulipristal acetate 5 mg daily for 12-weeks before planned surgery is effective in controlling bleeding, decreasing fibroid volume, and reducing discomfort in women with menorrhagia and anemia. Therefore, ulipristal acetate 5 mg has been approved for pre-surgical

treatment by the European Medicines Agency (EMA) in 2012 and thereafter by the Italian Medicines Agency (AIFA)[2].

Surgical treatments, currently indicated for these benign tumors, include hysterectomy and myomectomy and both are invasive procedures. At present, the drugs approved for the pre-surgical treatment include Gonadotropin-Releasing Hormone (GnRH) analogues and ulipristal acetate [3]. Choice of the treatment is closely related to the attitudes of gynecologists [4].

The main aim of our work was to evaluate the pharmacoeconomic profile in Italy of a single-13-week cycle of ulipristal acetate 5 mg daily in comparison with placebo before surgery for the management of symptomatic uterine fibroids.

Our pharmacoeconomic analysis was aimed at determining the costs incurred by patients treated or not treated with ulipristal acetate 5 mg/day; a Markov model was developed for this purpose.

### Materials and methods

#### PEARL-I trial

In this randomized trial, women with symptomatic fibroids, excessive uterine bleeding (a score of >100 on the pictorial blood-loss assessment chart [PBAC, an objective assessment of blood loss,

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in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding]) and anemia (hemoglobin level of  $\leq 10.2$  g per deciliter) were assigned to receive treatment for up to 13 weeks with oral ulipristal acetate at a dose of 5 mg per day (96 women) or 10 mg per day (98 women) or to receive placebo (48 women). All patients received iron supplementation. The co-primary efficacy end points were control of uterine bleeding (PBAC score of  $< 75$ ) and reduction of volume fibroid at week 13. Initially, all patients were eligible to undergo fibroid surgery, after ulipristal acetate treatment period, at week 13, patients could undergo surgery or not according to clinical judgment of the investigator. Clinical evaluation depended on co-primary end points, i.e. final reduction of fibroids volume and controlled uterine bleeding. According to the results of this trial, uterine bleeding at 13 weeks was controlled in 91% of the women receiving 5 mg of ulipristal acetate, 92% of those receiving 10 mg of ulipristal acetate, and 19% of those receiving placebo ( $p < 0.001$  for the comparison of each dose of ulipristal acetate with placebo). The rates of amenorrhea were 73%, 82%, and 6%, respectively, with amenorrhea occurring within 10 days in the majority of patients receiving ulipristal acetate. The median changes in total fibroid volume were  $-21\%$ ,  $-12\%$ , and  $+3\%$  (all differences being statistically significant compared with placebo). The conclusion of this trial was that treatment with ulipristal acetate for 13 weeks effectively controls excessive bleeding due to uterine fibroids and reduces the size of the fibroids prior to surgery.

#### Pharmacoeconomic analysis

To determine the incremental cost-effectiveness ratio (ICER) of preoperative ulipristal acetate, a model-based pharmacoeconomic analysis was carried out. For this purpose, the standard equation of ICER was applied [6]:

$$\text{ICER} = \frac{(C_{\text{innovative treatment}} - C_{\text{comparator}})}{(\text{QALYs}_{\text{innovative treatment}} - \text{QALYs}_{\text{comparator}})} \quad (1)$$

where innovative treatment is ulipristal acetate 5 mg for 13 weeks, comparator is placebo, C indicates cost per patient, and QALYs indicates quality-adjusted life years per patient.

Data of incremental cost and incremental effectiveness evaluated through the above equation were estimated as indicated below.

#### Efficacy data

Efficacy data were meant to be those reported in the PEARL-1 trial; in particular, the efficacy data extracted from this randomized trial were translated into QALYs according to an analysis published by Messori [5].

#### Cost analysis

Our analysis was based on a societal perspective and therefore included both direct and indirect costs. Unit costs for drugs, diagnostics, hospitalization, specialist consultations and surgeries are listed in Table 1. This information (adapted to the Italian setting) was drawn from a series of studies published over the past years. All costs were expressed in €.

#### Economic modeling

Our Markov model included two simulation procedures designed to estimate costs for treated and untreated patients, respectively. The procedure designed to handle costs was separately run using the parameters of ulipristal acetate and those of placebo. These two markovian simulations generated the two values reported in the numerator of Eq. (1) (incremental cost per patient).

Markov model. Our analysis employed a Markov model directly based on the PEARL-I trial. Hence, the model was designed to compare patients receiving ulipristal acetate 5 mg for 13 weeks with those receiving placebo. The simulation model was developed using a commercial software (TreeagePro, Treeage Software Inc., 2011 version, Williamstown, MA, USA). The Markov analysis traced the number of cycles evaluated in the iterative process. The main characteristics of the model are presented in Fig. 1. Further details are presented in Appendix A.

Briefly, the core of both our simulation model is a decision node from which several branches originate. Among these, a branch with transition probability equal to 1 (denoted with the abbreviation “upa 1 cycle” in Fig. 1) represents the transition through which all patients are assumed to move, whereas the other 6 branches of the model represent the various pathways that patients can enter later on. Hence, a total of 7 different health states are included in the Markov model.

The transition probabilities that manage how patients move across the health states are presented in Fig. 1. Probabilities with values of 0 or 1 are self-explanatory; the symbol “#” identifies a probability equal to the value needed to reach 100% after taking into account the other probability/probabilities expressed in numerical form and assigned to the other branch(es) of the same node. (see Appendix A for further details).

According to the Markov approach, costs incurred in the model are iteratively summed upon each cycle. The items described in Table 1 participated in the cost analysis.

As regards the syntax of the Treeage software, cost data were handled as “incremental rewards” (denoted as “Incr Rwd”). In other words, the variable “Rewards” was used to cumulate the various cost data at each cycle.

**Table 1**  
Model parameters employed in our basecase analysis.

Model parameter	Value	Source
Length of 1 cycle	1 week	–
Women’s age upon enrolment (base case analysis)	42 years	PEARL-I randomized trial (Donnez et al. [1])
Women’s life expectancy	See our demographic life expectancy table	ISTAT [7]
Rate of controlled bleeding	91% for ulipristal vs 19% for placebo	PEARL-I randomized trial (Donnez et al. [1])
Cost of 13 weeks of ulipristal treatment (direct costs)	€405.63	Table II of Maratea [8]
Cost of 13 weeks of ulipristal treatment (indirect costs)	€20.92	Table II of Maratea [8]
Cost of 13 weeks of ulipristal treatment (indirect plus direct costs)	€405.63 + €20.92 = €426.55	–
Cost of an episode of uncontrolled bleeding (direct costs)	€75.15	Table 3 of Nagy et al. [9]
Cost of an episode of uncontrolled bleeding (indirect costs)	€31.38	Table II of Maratea [8]
Cost of an episode of uncontrolled bleeding (indirect plus direct costs)	€75.15 + €31.38 = €106.53	–
Cost of surgery	€3500	Di Carlo et al. [10]

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