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Economic impact of ulipristal acetate
on surgical procedures for uterine fibroids in France

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- No other relationships or activities that could appear to have influenced the submitted work.

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The Corresponding Author, Pr. Hervé FERNANDEZ, assures that all authors included on the paper fulfil the criteria of authorship, and that there are no other persons who satisfied the criteria of authorship but are not listed. Each author had the following role:

	Design of the work	Analysis of data & modeling	Interpretation of results	Writing of the paper & proofreading
Hervé FERNANDEZ	✓		✓	✓
Olivier JOURDAIN	✓		✓	✓

Vincent VILLEFRANQUE	✓		✓	✓
Matthieu LEHMANN	✓	✓	✓	✓
Antoine LAFUMA	✓	✓	✓	✓
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The submitted work was integrally achieved by the authors, organized as an independent committee gathering experts in uterine fibroids and technical specialists in health technology assessment.

Access to data:

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration:

The Corresponding Author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing:

Budget Impact Model, developed under Microsoft Excel, available with open access from the Corresponding Author at herve.fernandez@aphp.fr

Relevant reporting statement:

CHEERS checklist, which is rather recommended for medico-economic analyses, is not suitable for budget impact analyses. However, the budget impact model was developed in accordance with the Principles of Good Practice for budget impact analysis¹ issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). These guidelines can be consulted on the ISPOR website.

Statistical packages:

- SAS v9.3 for data analysis;
- Microsoft Excel for modeling.

1 Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, Orlewska E, Penna P, Rodriguez Barrios JM, Shau WY. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health*. 2014 Jan-Feb;17(1):5-14. doi:10.1016/j.jval.2013.08.2291. PubMed PMID: 24438712.

ABSTRACT

Objective. To assess the financial impact of using ulipristal acetate 5 mg (UPA) to treat women with uterine fibroids (UF) causing moderate to severe symptoms.

Design. We modeled trends in the number of surgical procedures for symptomatic UF, with and without the use of UPA for preoperative or intermittent treatment, and assessed the financial impact of UPA use from the French national healthcare insurance system perspective.

Setting. A French national hospital database (PMSI) that records admissions and relative procedures to public and private hospitals.

Participants. Women eligible for surgical procedures for UF.

Main outcome measures. Cost benefits of UPA treatment.

Results. This study based on observational retrospective data shows that the current use of UPA in its preoperative indication was associated with 5645 fewer surgeries from 2013 to 2015. Extrapolation suggests 17 884 fewer surgeries from 2016 to 2019. Overall, preoperative use of UPA results in substantial cost savings for the French national healthcare insurance system, with a cumulated budget impact estimated at -5.0 M€ from 2013 to 2015 and -15.7 M€ from 2016 to 2019. In addition, treating women nearing the menopause (>48 years) with intermittent treatment from 2017 to 2019 could produce an incremental cost-saving of 18.8 M€.

Conclusions. This study shows that the use of UPA in women eligible for surgical procedures for UF is associated with considerable savings for the French national healthcare insurance system in both preoperative and intermittent indications by decreasing the need to perform surgeries.

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3 **Keywords:** Uterine fibroids; Selective progesterone receptor modulator; Ulipristal acetate;
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5 Surgery; Hysterectomy; Myomectomy; Economic evaluation; Budget impact.
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STRENGTHS AND LIMITATIONS OF THIS STUDY

- Analysis based on exhaustive real-world data available in French national databases;
- Consistent and robust conclusions of the analysis (ulipristal acetate is cost-saving), even during sensitivity analysis and considering the worst-case scenario;
- Conservative approach, by excluding indirect costs associated to sick leave (which are partially compensated by the French national healthcare system) and by limiting the market penetration of UPA as a pre-surgical treatment;
- Inflection point in the number of surgeries seen at the time of launch of UPA, solely attributed to the efficacy of UPA;
- Exploratory scenario for intermittent indication, due to limited availability of real-world data related to the use of intermittent UPA in routine practice.

INTRODUCTION

Uterine fibroids (UF), also known as leiomyomas or myomas, are frequent benign smooth-muscle tumors of the uterus. They are estimated to affect 20–40% of women during reproductive years, with large variations from one population to another.¹ Most women with UF have no symptoms, but UF can cause abnormal and excessive uterine bleeding, infertility, pelvic pain, dysmenorrhea and/or anemia, thereby undermining quality of life.² In a 2009 European survey, the prevalence of self-reported UF in France was 4.6%.³

Despite the associated risks, hysterectomy is necessary for some patients with UF, whereas a more conservative approach can be considered for other women, depending on factors such as age, the wish for future pregnancy, characteristics of the fibroids, symptom severity, and patient preferences.⁴ Recently, selective progesterone receptor modulators (SPRM) have been developed as therapeutic options for treatment of moderate to severe symptoms of UF. One SPRM, ulipristal acetate 5 mg (ESMYA[®]), has been shown to significantly reduce uterine bleeding and myoma volume.⁵⁻⁶ The “PEARL series” of clinical studies demonstrated the efficacy and safety of oral UPA in women with symptomatic uterine fibroids.⁷⁻⁸⁻⁹⁻¹⁰

Based on the results of PEARL I and II⁷⁻⁸, UPA was first approved in February 2012 by the European Medicines Agency (EMA) for preoperative treatment of moderate to severe symptoms of UF in adult women of reproductive age with a treatment duration limited to 3 months.¹¹ Reimbursement status was granted by the French Ministry of Health and Welfare in 2013 for one 3-month treatment course¹²⁻¹³, and UPA started to be marketed for this preoperative indication in August 2013.

In the PEARL II study, about half the patients treated with either ulipristal acetate or leuprolide acetate did not undergo surgery at the end of their medical treatment. Exploratory analysis of these patients showed that their fibroids began to regrow about one month after the

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3 last dose of leuprolide acetate, whereas the fibroid volume reduction was maintained at least
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5 up to 6 months after the end of treatment in most patients who received UPA.¹⁴
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8 Recently, the PEARL IV study compared 5-mg and 10-mg doses of UPA administered as
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10 repeated intermittent treatment (up to four 3-month courses, with breaks of 2 months, for a
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12 total study duration of 21 months). Uterine bleeding was controlled in respectively 73.3% and
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14 75.0% of patients in the two groups at the end of the 4th course. After 4 courses, myoma
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16 volume fell by 67.0% in the 5-mg group and by 70.4% in the 10-mg group, a non-statistically
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18 significant difference. Efficacy was maintained during the off-treatment periods.¹⁰
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21 Consequently, in April 2015, EMA extended the indications for UPA to cover repeated
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23 intermittent treatment courses of 3 months each in adult women of reproductive age with
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25 moderate to severe symptoms from uterine fibroids.¹⁵ However, this indication is not yet
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27 reimbursed by the French national healthcare insurance system.
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31 Although clinical data suggest a positive impact of UPA on the need for surgery among
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33 women with symptomatic uterine fibroids, its economic impact has not been documented. The
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35 objective of this study was to assess the budget impact of UPA at the level of the French
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37 population, from the point of view of the national healthcare insurance system.
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METHODS

The budget impact of UPA was estimated by using a dedicated model constructed in Microsoft Excel, in accordance with the Principles of Good Practice for budget impact analysis issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).¹⁶ Based on real-world data, we assessed the economic impact of UPA in women with moderate to severe uterine fibroids who were eligible for surgical procedures. This study population corresponds to the conditions of UPA reimbursement by the French national healthcare insurance system for the preoperative indication, and to the most severe cases of intermittent indication granted by EMA.

Even though UPA shows substantial benefits in the segment of the intermittent indication not directly concerned by immediate surgical procedures, this population was not included in the analysis. Indeed, given the lack of real-world data for this population, theoretical analysis of the benefits associated with intermittent treatment would have been poorly informative. The study population represented about 10% of the estimated total population of women with moderate to severe uterine fibroids in France (307 000 patients, including women having surgical procedures).

The economic benefits associated with the use of UPA in the study population were measured in terms of the impact of UPA on the use of surgery, and compared to treatment costs in order to estimate the budget impact.

A counterfactual scenario was used to assess the hypothetical use of surgery in France if UPA had not been available from August 2013. The following two scenarios were then compared to this counterfactual scenario:

1. The current scenario, based on the use of surgery with UPA available in its current marketing situation in France (i.e. the preoperative indication since August 2013);

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3 2. An exploratory scenario modeling the potential incremental impact associated with the
4 reimbursement of intermittent UPA after January 2017 concerning surgical treatment.
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8 In this analysis, the benefits of intermittent indication were limited to the possibility of
9 postponement of the surgery after the occurrence of menopause and, consequently, of
10 avoidance of surgery. As the PEARL IV study¹⁰ evaluated the efficacy of intermittent
11 treatment over a 2-year duration of exposure, the impact of intermittent UPA was only
12 assessed in women nearing the menopause (>48 years).
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19 In all three scenarios, outcomes were estimated from exhaustive real-world data available in
20 French national databases. The perspective was that of the French national healthcare
21 insurance system (*Caisse Nationale d'Assurance Maladie*; CNAM). Healthcare costs
22 associated with reimbursed UPA treatment units (standard packs of 28 pills) and surgical
23 procedures were considered. A time horizon of 7 years was chosen (2013-2019) in order to
24 assess the impact of both UPA indications on the surgical management of UF, from the
25 market introduction of preoperative treatment to the end of a 3-year period of intermittent
26 treatment availability.
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37 **Identification of surgical procedures in national databases**

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39 The number of surgical procedures for UF was estimated from the database of the French
40 Medical Information System (*Programme de Médicalisation des Systèmes d'Information*;
41 PMSI), which covers all French public and private hospitals. All hospital stays in a given year
42 are available in standardized discharge reports and are collected in the PMSI database. This
43 database is primarily used for invoicing purposes through a DRG system by hospitals to
44 CNAM, but it can also be used to assess the number of patients treated per year for a specific
45 disease, and the number of hospital stays per patient. This database is used for
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3 epidemiological purposes by several public health organizations, such as the National Cancer
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5 Institute (*Institut National du Cancer*; INCa).
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8 Hospital stays for uterine fibroids were extracted from the PMSI database by using the ICD-
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10 10 codes for uterine fibroids, namely D25 (leiomyoma of uterus); D25.0 (submucous
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12 leiomyoma of uterus); D25.1 (intramural leiomyoma of uterus); D25.2 (subserosal leiomyoma
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14 of uterus) and D259 (leiomyoma of uterus, unspecified). The surgical procedures were
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16 selected from the PMSI by selecting the specific codes of the French procedure classification
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18 (*Classification Commune des Actes médicaux*; CCAM), as shown in **Table 1**.
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21 **Historical data on the use of surgery for uterine fibroids**

22 The PMSI data revealed two periods with respect to UF surgery:
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- 25 • Before the availability of UPA, from January 2007 to August 2013, when the annual
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27 number of UF surgeries was tending to rise;
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- 30 • After the availability of UPA for preoperative use (August 2013 to 2015), when the
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32 annual number of UF surgeries tended to fall.
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37 In the counterfactual scenario, assuming non use of UPA, the trend observed before market
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39 release in France was extrapolated from August 2013 to 2019 by using linear regression and
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41 data recorded from January 2007 to August 2013 (+132 surgical procedures per year on
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43 average).
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46 In the current scenario, with preoperative use of UPA, the trend in UF surgery after UPA
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48 market release in France was extrapolated to 2016 by using linear regression and data
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50 collected from August 2013 to the end of 2015 (-1132 surgical procedures per year on
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52 average). Adopting a conservative approach, we postulated that market penetration of UPA as
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54 a preoperative treatment would reach a plateau at the end of 2016, and that trends in the
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number of surgical procedures, both with and without preoperative use of UPA, would be identical from that point onwards.

The numbers of surgeries performed in the two scenarios over the studied time horizon are shown in **Table 2**.

The number of surgical procedures avoided through preoperative UPA treatment in the current scenario was measured as the difference in the number of surgical procedures performed in the current and counterfactual scenarios.

Historical data on preoperative UPA therapy

The use of UPA in its current marketing situation (preoperative indication only) was assessed by analyzing exhaustive drug reimbursement claims (Medic'AM) provided by the French national healthcare insurance system.¹⁷ The numbers of treatment units reimbursed in 2013, 2014 and 2015 were 5328, 34 956 and 54 076, respectively. These treatment units correspond to respectively 2220, 12 227 and 18 552 treatment initiations. These estimates were based on the following hypotheses: 1) all treatment units were sold for the preoperative indication; 2) each patient took 3 treatment units; and 3) treatment initiations were smoothed over time.

For subsequent years, sales data for 2016 were extrapolated from actual data recorded up to May 2016, and it was assumed that market penetration would be maximal in this indication by the end of 2016 (stabilization of the number of treatment initiations in the preoperative indication). The extrapolated numbers of treatment units were 73 280 for 2016 and 74 882 for each year from 2017 to 2019, corresponding to 24 961 treatment initiations per year between 2016 and 2019. In other words, we extrapolated that about two-thirds of scheduled surgeries between 2016 and 2019 would be preceded by UPA treatment.

Exploratory scenario with the intermittent UPA indication

The dose regimen considered for intermittent treatment in this analysis was that used in the PEARL IV trial, i.e. four 3-month courses separated by a drug-free period until the start of the second menstrual period after the end of the previous course (approximately 2 months), with 3 months of follow-up after the 4th course (total study duration 21 months). The impact of intermittent indication on surgical procedures depends mainly on the age at which UPA treatment starts. When prescribed to a woman nearing the menopause, UPA could suppress symptoms and result in postponement of surgery until beyond the menopause, when it would no longer be necessary for most women. Under these assumptions, UPA can be considered a relevant alternative to surgery.

Within this framework, the budget impact of the intermittent indication in the study population was estimated under the assumption that UPA would be prescribed first to women nearing the menopause (>48 years) during the period 2017 to 2019, with the objective of avoiding surgery.

In this scenario, as the aim of intermittent treatment is to avoid surgery and, consequently, preoperative treatment, the benefits of preoperative treatment were estimated after taking into account surgical procedures avoided through the use of intermittent treatment. Thus, this exploratory analysis was modeled on the estimated number of surgical procedures in the counterfactual scenario.

Starting with the number of surgical procedures that would be done if UPA was not available (37 466 in 2017, 37 598 in 2018 and 37 729 in 2019), we estimated that:

- 31% of these procedures would have involved women over 48 years old (analysis of the PMSI database showed that age at surgery was stable);

- Respectively 20%, 40% and 60% of the surgeries warranted for women over 48 years old in 2017, 2018 and 2019 would have been avoided by intermittent UPA treatment, assuming market penetration similar to that observed for preoperative UPA during the first 3 years on the French market.

On this basis, the estimated numbers of women who would be prescribed intermittent treatment were 2348 in 2017, 4712 in 2018 and 7093 in 2019.

By smoothing those initiations uniformly over the year, the estimated numbers of treatment units reimbursed for intermittent treatment were 10 566 in 2017, 36 468 in 2018 and 64 899 in 2019.

The annual number of surgical procedures would be reduced by the number of intermittent treatment initiations. At the end of intermittent UPA treatment, surgery was only supposed to proceed when the menopause did not occur during the treatment sequence. The probability that the menopause would occur during intermittent UPA treatment was based on information provided by the French National Authority for Health (*Haute Autorité de Santé*; HAS)¹⁸, which reports that respectively 7%, 33% and 83% of women in the 40-44, 45-49 and 50-54 year age groups are postmenopausal. Nearly all French women over 60 years of age are postmenopausal. By matching the beta distribution with the proportions reported by HAS, we estimated that the average probability of menopause occurrence during UPA treatment was 59% among women over 48 years of age.

Taking into account intermittent treatment initiations, the resulting deferral of surgery, and the cancellation of surgery in 59% of cases at the end of UPA treatment, we estimated that respectively 35 118, 33 128 and 31 851 women would be scheduled for UF surgery in 2017, 2018 and 2019. A graphical representation of the calculation is shown in **Figure 1**.

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3 Finally, the subsequent impact of preoperative treatment was modeled in women eligible for
4 surgery who did not start intermittent treatment during the study period (35 118 in 2017, 32
5 885 in 2018, and 30 636 in 2019). Based on the proportion of surgeries preceded by
6 preoperative treatment, and the proportion of surgeries avoided after preoperative treatment in
7 the current scenario, we estimated that respectively 23 396, 21 832 and 20 268 women would
8 be prescribed preoperative treatment, resulting in 4191, 3911 and 3631 surgeries avoided in
9 2017, 2018 and 2019, respectively. The estimated numbers of treatment units reimbursed for
10 this indication in the exploratory scenario were 70 580 in 2017, 65 887 in 2018 and 61 195 in
11 2019.

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14 By jointly considering the outcomes measured in both indications, the estimated number of
15 surgical procedures in the exploratory scenario was 30 927 in 2017, 29 217 in 2018 and 28
16 221 in 2019, with respectively 81 146, 102 355 and 126 094 UPA treatment units reimbursed
17 over this period.

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20 The number of surgical procedures avoided by the use of UPA in both its indications was
21 estimated in the exploratory scenario as the difference in the number of surgical procedures
22 performed between the exploratory and counterfactual scenarios.

23 24 25 **Cost of surgical procedures**

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27 For public hospitals, the costs of surgical procedures were calculated from 2015 public
28 diagnosis-related group (DRG) tariffs.¹⁹ Private hospitals use the 2015 private diagnosis-
29 related group (DRG) tariffs¹⁹, to which physician's fees were added²⁰, as they are not included
30 in private DRG tariffs and are reimbursed on a fee-for-service basis. The estimated average
31 cost of a surgical procedure for uterine fibroids was 2416 € (SD=1126). Surgical procedures
32 are fully reimbursed by the French national healthcare insurance system.

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35 Detailed costs are shown in **Table 3** according to the type of surgery and route.

Assessment of the budget impact

The costs and benefits resulting each year from the current and exploratory scenarios was computed by taking the following steps:

- The costs avoided through lesser use of surgery were estimated by multiplying the number of surgical procedures avoided in the relevant scenario by the total average cost of one surgical procedure;
- The amount reimbursed to patients by the French national healthcare insurance system for the use of UPA in the relevant scenario was estimated from the annual number of reimbursed treatment units in the relevant scenario, the public price of UPA, and a 65% patient reimbursement rate.

Finally, the budget impact in each scenario was calculated as the difference between the amount reimbursed for UPA by the French national healthcare insurance system in the relevant scenario and the costs avoided through lesser use of surgery.

Sensitivity analyses

The sensitivity of the cumulative budget impact from 2013 to 2019 for each indication (preoperative and intermittent use) to the principal parameters was assessed in deterministic sensitivity analyses, in which each of the following parameters was varied individually:

- Number of surgical procedures: the bounds of the 95 percent confidence intervals for regression coefficients used to extrapolate the number of surgical procedures with and without preoperative UPA were used to derive potential worst-case and best-case scenarios for UPA. In the best-case scenario, the trend without UPA was maximized (+177 surgical procedures per year) and the trend with UPA was minimized (-1207 surgical procedures per year). In the worst-case scenario, the trend without UPA was

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3 minimized (+86 surgical procedures per year) and the trend with UPA was maximized (-
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5 1057 surgical procedures per year);
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9 • Budget impact from the societal perspective: each year, a study organized by the French
10 Agency for Information on Hospital Care (*Agence Technique de l'Information sur*
11 *l'Hospitalisation*; ATIH) estimates the costs associated with hospital stays from a societal
12 perspective, using an analytical accounting system in a sample of French hospitals.²¹
13 Using data from this study, we estimated that the total average cost of a surgical procedure
14 was 2810 €. In keeping with the societal perspective, total UPA treatment costs were
15 considered in this analysis, rather than the portion reimbursed by CNAM;
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- 18 • Indirect costs associated with sick leave: one particularity of the French national
19 healthcare system is partial compensation for sick leave. The national database
20 (DAMIR)²² gathering all expenditures of the French national healthcare insurance system
21 allowed us to estimate the average daily compensation for sick leave at 31 €. By taking
22 into account an average 30-day period of sick leave after UF surgery²³ and an employment
23 rate of 92% among women with uterine fibroids²⁴, the average cost of sick leave after UF
24 surgery was estimated at 856 €;
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- 27 • Duration of exposure during intermittent treatment: based on the PEARL II results
28 showing a maintenance of the effect of UPA on UF size and no return to initial symptoms
29 severity scores 6 months after treatment, and on PREMYA²⁵ results confirming the
30 satisfaction of both patients and healthcare professionals at least 6 months after treatment
31 cessation, the off-treatment periods and the follow-up period were both extended to 6
32 months. The total duration of UPA exposure during intermittent treatment was therefore
33 expanded to 36 months. This assumption has an impact on the probability of menopause
34 occurring during intermittent treatment and the age at which intermittent treatment can be
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3 prescribed with the objective of avoiding surgery. Accordingly, intermittent treatment was
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5 supposed to be prescribed in women over 47 years of age in this analysis.
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RESULTS

Current scenario

From 2013 to 2015, 94 360 UPA treatment units were reimbursed by the French national healthcare insurance system for the preoperative indication, costing 8.7 M€. Over the same period, use of UPA was associated with 5645 fewer surgeries. The resulting cost saving was estimated at 13.6 M€.

From 2016 to 2019, the number of UPA treatment units reimbursed by the French national healthcare insurance system for the preoperative indication was extrapolated to 297 926 units, for a cost of 27.5 M€. Over the same period, extrapolation suggested 17 884 fewer surgeries, saving 43.2 M€.

Finally, the estimated cumulative budget impact of preoperative UPA from 2013 to 2019 was -20.6 M€. Detailed annual results are shown in **Table 4**. The number of surgeries performed in each scenario is shown on a larger timeframe in **Figure 2**.

Exploratory scenario

From 2013 to 2016, the exploratory and current scenarios produced the same outcomes, with an estimated cumulative UPA budget impact of -9.0 M€ over the period.

From 2017 to 2019, by comparison with the current scenario, the arrival of intermittent UPA treatment in the exploratory scenario was associated with an increase in the number of reimbursed treatment units and in the number of surgical procedures avoided. With 309 596 treatment units reimbursed from 2017 to 2019 in the exploratory scenario, we estimate that treatment costs in the study population would increase by 37.8% after the arrival of intermittent UPA, cumulating at 28.6 M€ over the period. On the other hand, we estimated that the number of surgical procedures avoided from 2017 to 2019 would increase by 82.1%

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3 after the arrival of intermittent UPA, resulting in a cost saving of 59.0 M€ over the period.
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5 Overall, the cumulative budget impact of UPA from 2017 to 2019 in this scenario was
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7 estimated at -30.4 M€.
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10 Finally, the cumulative budget impact of UPA in both indications from 2013 to 2019 was
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12 estimated at -39.4 M€. Detailed annual results are shown in **Table 5**. The number of surgeries
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14 performed in each scenario is shown on a larger timeframe in **Figure 2**.
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17 Over the studied time horizon, the cost benefit of UPA is due jointly to the increasing market
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19 penetration of intermittent treatment and to the deferral of surgery. Over the long term, when
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21 prescriptions for intermittent treatment have stabilized, the economic benefits associated with
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23 the intermittent indication will be entirely driven by the number of surgeries that are cancelled
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25 because of menopause occurrence. However, with an average 59% probability of menopause
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27 occurrence during intermittent treatment, UPA is still expected to save costs for the French
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29 national healthcare insurance system over the long term, when prescribed to women over 48
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31 years old.
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34 35 **Sensitivity analyses** 36

37
38 The results were mostly sensitive to the extrapolation of the number of surgical procedures,
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40 the perspective, and surgical costs (**Table 6**). However, the use of UPA was always associated
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42 with considerable savings for the French national healthcare insurance system in both
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44 scenarios.
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DISCUSSION

This study based on observational retrospective data shows that the use of UPA in its first, preoperative indication resulted in substantial cost savings (5.0 M€) for the French national healthcare insurance system from 2013 to 2015. The corresponding savings extrapolated from 2016 to 2019 were 15.7 M€. The incremental benefits associated with the intermittent treatment indication were estimated at 18.8 M€ from 2017 to 2019. However, the economic benefits of intermittent treatment are likely to decrease over time, due to stabilization of prescriptions and to a lesser impact of temporary deferral of surgery. Even in the long term, intermittent treatment is expected to save costs for the French national healthcare insurance system in the study population by offering a curative medical option for perimenopausal women.

There are no comparable pharmacoeconomic evaluations of UPA in the literature. An Italian study²⁶ compared intermittent use to preoperative use, estimating the incremental cost-effectiveness ratio (ICER) between the two strategies and the budget impact of intermittent treatment. The authors concluded that, compared to former preoperative use, intermittent UPA therapy had a favorable pharmacoeconomic profile and was cost-saving for the national healthcare system. Our results are consistent with these findings, as we found that intermittent treatment was associated with more substantial benefits than preoperative treatment in comparable marketing conditions.

The budget impact of the preoperative indication reported here is based on real-world data recorded in France at the national level and on conservative economic assumptions. During the observation period, no other explanation was found for the inflexion point noted when UPA was first marketed: extrapolation of the cost benefit of this first indication to future

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3 years was less factual, but we adopted a conservative approach by assuming that prescriptions
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5 would plateau.
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8 More assumptions were used for the exploratory scenario, and the estimates are therefore less
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10 robust. However, the cost benefits associated with surgery avoidance through the use of
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12 intermittent treatment depended on the probability of menopause occurring during the UPA
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14 treatment sequence. The results of the PEARL II study, confirmed by real-world data in the
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16 PREMYA study, suggest that this approach is conservative, as efficacy and satisfaction
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18 persisted during a 6-month follow-up period. In routine practice, the precise level of cost
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20 savings will depend on effective UPA usage by physicians, and on the ability to adjust the
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22 dose regimen to the individual patient. Also, some patients could be treated for longer than
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24 expected, depending on symptoms occurrence and the wish of the patient to avoid or postpone
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26 surgery.
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30 The present evaluation was limited to a portion of the therapeutic area targeted by intermittent
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32 treatment. As UPA can control UF symptoms for long periods, intermittent treatment is likely
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34 to be increasingly prescribed to women with less severe symptoms, including younger
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36 patients with childbearing potential.
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40 Too little real-world information is available to address the use of intermittent UPA in routine
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42 practice, whereas the impact of preoperative treatment on the use of surgery has been robustly
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44 quantified. Analyses of intermittent UPA treatment based on French medical-administrative
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46 databases will help answer this question.
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TABLES

Table 1. CCAM codes used to identify surgical procedures within the PMSI.

Access route	Hysterectomy	Myomectomy	Embolization
Vaginal	JKFA005; JKFA026		
Laparoscopy	JKFA006; JKFA018 JKFC002; JKFC005 JKFC006	JKFC001; JKFC004	
Laparotomy	JKFA015; JKFA024 JKFA028; JKFA032	JKFA016; JKFA022	
Hysteroscopy		JKFE002	
Intra-arterial			EDSF004; EDSF014

Table 2. Numbers of surgical procedures in the counterfactual and current scenarios.

	2013	2014	2015	2016	2017	2018	2019
Counterfactual scenario without UPA	36 940	37 071	37 203	37 335	37 466	37 598	37 729
Current scenario with preoperative UPA	36 216	35 129	34 224	32 863	32 995	33 127	33 258

Table 3. Average cost of surgical procedures according to the type of surgery and route in 2015.

Access route	Hysterectomy	Myomectomy	Embolization
Vaginal	2975 € (N = 4966)		
Laparoscopy	3040 € (N = 5476)	2434 € (N = 1706)	
Laparotomy	3283 € (N = 7566)	2604 € (N = 3523)	
Hysteroscopy		1154 € (N = 10333)	
Intra-arterial			1786 € (N = 654)

Table 4. Budget impact of preoperative UPA treatment in the current scenario.

	2013	2014	2015	2016	2017	2018	2019
Treatment costs resulting from the use of UPA							
Number of reimbursed treatment units	5328	34 956	54 076	73 280	74 882	74 882	74 882
Amount reimbursed by the French national healthcare insurance system (M€)	0.5	3.2	5.0	6.8	6.9	6.9	6.9
Surgical procedures avoided by the use of UPA							
Number of surgical procedures avoided	724	1942	2979	4471	4471	4471	4471
Cost saving (M€)	1.7	4.7	7.2	10.8	10.8	10.8	10.8
Budget impact of UPA							
Annual (M€)	-1.3	-1.5	-2.2	-4.0	-3.9	-3.9	-3.9
Cumulative (M€)	-1.3	-2.7	-5.0	-9.0	-12.9	-16.8	-20.6

Table 5. Budget impact of preoperative and intermittent UPA in the exploratory scenario.

	2013	2014	2015	2016	2017	2018	2019
Cost of UPA							
Number of reimbursed treatment units	5328	34 956	54 076	73 280	81 146	102 355	126 094
Amount reimbursed by the French national healthcare insurance system (M€)	0.5	3.2	5.0	6.8	7.5	9.5	11.7
Surgical procedures avoided by the use of UPA							
Number of surgical procedures avoided	724	1942	2979	4471	6539	8380	9508
Costs avoided (M€)	1.7	4.7	7.2	10.8	15.8	20.2	23.0
Budget impact of UPA							
Annual (M€)	-1.3	-1.5	-2.2	-4.0	-8.3	-10.8	-11.3
Cumulative (M€)	-1.3	-2.7	-5.0	-9.0	-17.3	-28.1	-39.4

Table 6. Sensitivity of the cumulative budget impact (M€) of UPA to the principal parameters from 2013 to 2019, in its two indications.

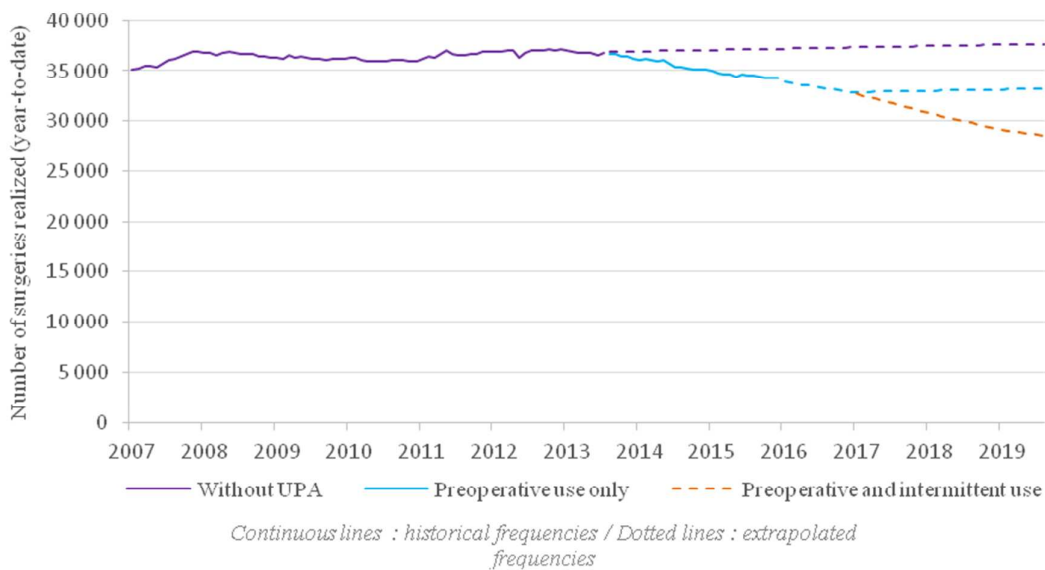
Scenario	Current scenario: Preoperative use only	Exploratory scenario: Both indications available
Reference analysis	-20.6	-39.4
Worst-case extrapolation of the number of surgeries	-4.8	-24.5
Best-case extrapolation of the number of surgeries	-36.4	-54.3
Budgetary impact from societal perspective	-10.4	-29.3
Indirect costs associated with sick leave	-40.8	-69.0
36-month intermittent treatment period	-20.6	-50.4

FIGURES

Figure 1. Calculation of the number of surgical procedures scheduled from 2017 to 2019, after taking into account the impact of intermittent UPA treatment.

35 118 surgeries scheduled in 2017	33 128 surgeries scheduled in 2018	31 851 surgeries scheduled in 2019
=	=	=
37 466 surgeries done without UPA in 2017	37 598 surgeries done without UPA in 2018	37 729 surgeries done without UPA in 2019
-	+	+
2348 intermittent UPA treatment initiations in 2017	243 surgeries from 2017 deferred to 2018	728 surgeries from 2017 deferred to 2019
$2348 = 37466 * P_{age\ group} * 20\%$	$2348 * 25\%^{[1]} * (1 - P_{menopause})$	$2348 * 75\%^{[1]} * (1 - P_{menopause})$
	-	+
	4712 intermittent UPA treatment initiations in 2018	487 surgeries from 2017 deferred to 2018
	$4712 = 37598 * P_{age\ group} * 40\%$	$4712 * 25\%^{[1]} * (1 - P_{menopause})$
		-
		7093 intermittent UPA treatment initiations in 2019
		$7093 = 37729 * P_{age\ group} * 60\%$
<p>$P_{age\ group}$: proportion of surgeries involving women over 48 years old (31%)</p> <p>$P_{menopause}$: probability of menopause occurrence during UPA treatment among women over 48 years old (59%)</p> <p>[1] : smoothing of UPA initiations over the year implies that 25% (resp.75%) of surgeries in year Y are deferred to year Y+1 (resp.Y+2)</p>		

Figure 2. Assessment of the impact of UPA on the number of surgical procedures for uterine fibroids in both scenarios.



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Economic impact of ulipristal acetate
on surgical procedures for uterine fibroids in France

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Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare:

- Financial support for all authors from GEDEON-RICHTER for the submitted work;
- Financial relationship between Matthieu LEHMANN & GEDEON-RICHTER (employee);
- No other relationships or activities that could appear to have influenced the submitted work.

Authorship:

The Corresponding Author, Pr. Hervé FERNANDEZ, assures that all authors included on the paper fulfil the criteria of authorship, and that there are no other persons who satisfied the criteria of authorship but are not listed. Each author had the following role:

	Design of the work	Analysis of data & modeling	Interpretation of results	Writing of the paper & proofreading
Hervé FERNANDEZ	✓		✓	✓
Olivier JOURDAIN	✓		✓	✓

Vincent VILLEFRANQUE	✓		✓	✓
Matthieu LEHMANN	✓	✓	✓	✓
Antoine LAFUMA	✓	✓	✓	✓
Matthieu TRANCART	✓	✓	✓	✓

All authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere. However, the results were partially presented at the ISPOR 19th Annual European Congress in Vienna.

Identifiable patients:

The data used for submitted work did not involve individual-level information and do not allow the identification of individual patients.

Ethics approval:

Submitted work did not involve human participants and ethics approval was not required.

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GEDEON-RICHTER funded and was involved in the submitted work:

- Matthieu LEHMANN, employee of GEDEON-RICHTER, participated to the submitted work;
- In-house proofreading of the submitted work;
- Decision to submit the article for publication.

Independence of researchers from funders:

The submitted work was integrally achieved by the authors, organized as an independent committee gathering experts in uterine fibroids and technical specialists in health technology assessment.

Access to data:

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration:

The Corresponding Author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing:

Budget Impact Model, developed under Microsoft Excel, available with open access from the Corresponding Author at herve.fernandez@aphp.fr

Relevant reporting statement:

CHEERS checklist, which is rather recommended for medico-economic analyses, is not suitable for budget impact analyses. However, the budget impact model was developed in accordance with the Principles of Good Practice for budget impact analysis^a issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). These guidelines can be consulted on the ISPOR website.

Statistical packages:

- SAS v9.3 for data analysis;
- Microsoft Excel for modeling.

a Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, Orlewska E, Penna P, Rodriguez Barrios JM, Shau WY. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health*. 2014 Jan-Feb;17(1):5-14. doi:10.1016/j.jval.2013.08.2291. PubMed PMID: 24438712.

ABSTRACT

Objective. To assess the budget impact of using ulipristal acetate 5 mg (UPA) to treat women with uterine fibroids (UF) causing moderate to severe symptoms.

Design. We modeled trends in the number of surgical procedures for symptomatic UF, with and without the use of UPA for preoperative or intermittent treatment, and assessed the budget impact of UPA use from the French national healthcare insurance system perspective.

Setting. A French national hospital database (PMSI) that records admissions and relative procedures to public and private hospitals.

Participants. Women eligible for surgical procedures for UF.

Main outcome measures. Economic impact of UPA treatment.

Results. This study based on observational retrospective data shows that the current use of UPA in its preoperative indication was associated with 5,645 fewer surgeries from 2013 to 2015. Extrapolation suggests 17,885 fewer surgeries from 2016 to 2019. Overall, preoperative use of UPA results in substantial cost savings for the French national healthcare insurance system, with a cumulated budget impact estimated at -5.0 M€ from 2013 to 2015 and -13.5 M€ from 2016 to 2019. In addition, treating women nearing the menopause (≥ 48 years old) with intermittent treatment from 2017 to 2019 could produce an incremental cost-saving of 19.0 M€.

Conclusions. This study shows that the use of UPA in women eligible for surgical procedures for UF is associated with considerable savings for the French national healthcare insurance system in both preoperative and intermittent indications by decreasing the need to perform surgeries.

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3 **Keywords:** Uterine fibroids; Selective progesterone receptor modulator; Ulipristal acetate;
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5 Surgery; Hysterectomy; Myomectomy; Economic evaluation; Budget impact.
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STRENGTHS AND LIMITATIONS OF THIS STUDY

- Analysis based on exhaustive real-world data available in French national databases;
- Consistent and robust conclusions of the analysis (ulipristal acetate is cost-saving), even during sensitivity analysis and considering the worst-case scenario;
- Conservative approach, by excluding indirect costs associated to sick leave (which are partially compensated by the French national healthcare system) and by limiting the market penetration of UPA as a pre-surgical treatment;
- Inflection point in the number of surgeries seen at the time of launch of UPA, solely attributed to the efficacy of UPA;
- Exploratory scenario for intermittent indication, due to limited availability of real-world data related to the use of intermittent UPA in routine practice.

INTRODUCTION

Uterine fibroids (UF), also known as leiomyomas or myomas, are frequent benign smooth-muscle tumors of the uterus. They are estimated to affect 20–40% of women during reproductive years, with large variations from one population to another.¹ Most women with UF have no symptoms, but UF can cause abnormal and excessive uterine bleeding, infertility, pelvic pain, dysmenorrhea and/or anemia, thereby undermining quality of life.² The prevalence of UF in France was estimated at 4.6% in a 2009 European survey³ (self-reported diagnosed UF in women aged between 15 and 49 y-o.) and 8.8% in a 2014 French survey⁴ (diagnosed symptomatic UF in women aged between 30 and 55 y-o.).

Despite the associated risks, hysterectomy is necessary for some patients with UF, whereas a more conservative approach can be considered for other women, depending on factors such as age, the wish for future pregnancy, characteristics of the fibroids, symptom severity, and patient preferences.⁵ Recently, selective progesterone receptor modulators (SPRM) have been developed as therapeutic options for treatment of moderate to severe symptoms of UF. One SPRM, ulipristal acetate (UPA) 5 mg (ESMYA[®]), has been shown to significantly reduce uterine bleeding and myoma volume.⁶⁻⁷ The “PEARL series” of clinical studies demonstrated the efficacy and safety of oral UPA in women with symptomatic uterine fibroids.⁸⁻⁹⁻¹⁰⁻¹¹

Based on the results of PEARL I and II⁸⁻⁹, UPA was first approved in February 2012 by the European Medicines Agency (EMA) for preoperative treatment of moderate to severe symptoms of UF in adult women of reproductive age with a treatment duration limited to 3 months.¹² Reimbursement status was granted by the French Ministry of Health and Welfare in 2013 for one 3-month treatment course¹³⁻¹⁴, and UPA started to be marketed for this preoperative indication in August 2013.

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3 In the PEARL II study, about half the patients treated with either ulipristal acetate or
4 leuprolide acetate did not undergo surgery at the end of their medical treatment. Exploratory
5 analysis of these patients showed that their fibroids began to regrow about one month after the
6 last dose of leuprolide acetate, whereas the fibroid volume reduction was maintained at least
7 up to 6 months after the end of treatment in most patients who received UPA.¹⁵
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12 Recently, the PEARL IV study compared 5-mg and 10-mg doses of UPA administered as
13 repeated intermittent treatment (up to four 3-month courses, with breaks of 2 months, for a
14 total study duration of 21 months). Uterine bleeding was controlled in respectively 73.3% and
15 75.0% of patients in the two groups at the end of the 4th course. After 4 courses, myoma
16 volume fell by 67.0% in the 5-mg group and by 70.4% in the 10-mg group, a non-statistically
17 significant difference. Efficacy was maintained during the off-treatment periods.¹¹
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22 Consequently, in April 2015, EMA extended the indications for UPA to cover repeated
23 intermittent treatment courses of 3 months each in adult women of reproductive age with
24 moderate to severe symptoms from uterine fibroids.¹⁶ However, this indication is not yet
25 reimbursed by the French national healthcare insurance system.
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30 Although clinical data suggest a positive impact of UPA on the need for surgery among
31 women with symptomatic uterine fibroids, its economic impact has not been documented. The
32 objective of this study was to assess the budget impact of UPA at the level of the French
33 population, from the point of view of the national healthcare insurance system.
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METHODS

The budget impact of UPA was estimated by using a dedicated model constructed in Microsoft Excel, in accordance with the Principles of Good Practice for budget impact analysis issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).¹⁷ Based on real-world data, we assessed the budget impact of UPA in women with moderate to severe uterine fibroids who were eligible for surgical procedures. This study population corresponds to the conditions of UPA reimbursement by the French national healthcare insurance system for the preoperative indication, and to the most severe cases of intermittent indication granted by EMA.

Even though UPA shows substantial benefits in the segment of the intermittent indication not directly concerned by immediate surgical procedures, this population was not included in the analysis. Indeed, given the lack of real-world data for this population, theoretical analysis of the benefits associated with intermittent treatment would have been poorly informative. The study population represented about 10% of the estimated total population of women with moderate to severe uterine fibroids in France (307,000 patients, including women having surgical procedures).

The economic benefits associated with the use of UPA in the study population were measured in terms of the impact of UPA on the use of surgery, and compared to treatment costs in order to estimate the budget impact.

A counterfactual scenario was used to assess the hypothetical use of surgery in France if UPA had not been available from August 2013. The following two scenarios were then compared to this counterfactual scenario:

1. The current scenario, based on the use of surgery with UPA available in its current marketing situation in France (i.e. the preoperative indication since August 2013);

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3 2. An exploratory scenario modeling the potential incremental impact associated with the
4 reimbursement of intermittent UPA after January 2017 concerning surgical treatment.
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8 In this analysis, the benefits of intermittent indication were limited to the possibility of
9 postponement of the surgery after the occurrence of menopause and, consequently, of
10 avoidance of surgery. As the PEARL IV study¹¹ evaluated the efficacy of intermittent
11 treatment over a 2-year duration of exposure, the impact of intermittent UPA was only
12 assessed in women nearing the menopause (≥ 48 years old).
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19 In all three scenarios, outcomes were estimated from exhaustive real-world data available in
20 French national databases. The perspective was that of the French national healthcare
21 insurance system (*Caisse Nationale d'Assurance Maladie*; CNAM). Healthcare costs
22 associated with reimbursed UPA treatment units (standard packs of 28 pills) and surgical
23 procedures were considered. A time horizon of 7 years was chosen (2013-2019) in order to
24 assess the impact of both UPA indications on the surgical management of UF, from the
25 market introduction of preoperative treatment to the end of a 3-year period of intermittent
26 treatment availability.
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37 **Identification of surgical procedures in national databases**

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39 The number of surgical procedures for UF was estimated from the database of the French
40 Medical Information System (*Programme de Médicalisation des Systèmes d'Information*;
41 PMSI), which covers all French public and private hospitals. All hospital stays in a given year
42 are available in standardized discharge reports and are collected in the PMSI database. This
43 database is primarily used for invoicing purposes through a diagnosis-related group (DRG)
44 system by hospitals to CNAM, but it can also be used to assess the number of patients treated
45 per year for a specific disease, and the number of hospital stays per patient. This database is
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3 used for epidemiological purposes by several public health organizations, such as the National
4
5 Cancer Institute (*Institut National du Cancer*; INCa).
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8 Hospital stays for uterine fibroids were extracted from the PMSI database by using the ICD-
9
10 10 codes for uterine fibroids, namely D25 (leiomyoma of uterus); D25.0 (submucous
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12 leiomyoma of uterus); D25.1 (intramural leiomyoma of uterus); D25.2 (subserosal leiomyoma
13
14 of uterus) and D259 (leiomyoma of uterus, unspecified). The surgical procedures were
15
16 selected from the PMSI by selecting the specific codes of the French procedure classification
17
18 (*Classification Commune des Actes médicaux*; CCAM), as shown in **Table 1**.
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20 21 22 **Historical data on the use of surgery for uterine fibroids**

23
24 The PMSI data revealed two periods with respect to UF surgery (**Figure 1**):
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- 26
27 • Before the availability of UPA, from January 2007 to August 2013, when the annual
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29 number of UF surgeries was tending to rise;
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- 31
32 • After the availability of UPA for preoperative use (August 2013 to 2015), when the
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34 annual number of UF surgeries tended to fall.
35

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37 In contrast, the repartition of the age at surgery and the trends observed in the characteristics
38
39 of the hospitals stays (severity index, type of surgery) were sustained over the whole period
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41 (supplementary data available in **Appendix**).
42

43
44 The inflexion point in the number of surgeries observed at the time of launch of UPA was
45
46 solely attributed to the efficacy of UPA, as:
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- 48
49 • Both events (inflexion point and launch of UPA) were simultaneous;
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- 51
52 • There was no other emerging healthcare technology or public health decision which could
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54 have impacted the management or the incidence of moderate to severe uterine fibroids in
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56 France at this time.
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3 Within this context, two scenarios were compared (**Figure 1**):
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- 5 • The counterfactual scenario, assuming non use of UPA: the trend observed before market
6 release in France was extrapolated from August 2013 to 2019 by using linear regression
7 and data recorded from January 2007 to August 2013 (+132 surgical procedures per year
8 on average).
9
- 10 • The current scenario, with preoperative use of UPA: the trend in UF surgery after UPA
11 market release in France was extrapolated to 2016 by using linear regression and data
12 collected from August 2013 to the end of 2015 (-1,132 surgical procedures per year on
13 average). Adopting a conservative approach, we postulated that market penetration of
14 UPA as a preoperative treatment would reach a plateau at the end of 2016, and that trends
15 in the number of surgical procedures, both with and without preoperative use of UPA,
16 would be identical from that point onwards.
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30 The annual numbers of surgeries performed in the two scenarios over the studied time horizon
31 are shown in **Table 2**. Further details about the linear extrapolation of the number of surgeries
32 (initial data, regression coefficients and extrapolation results) are provided in **Appendix**.
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35 The number of surgical procedures avoided through preoperative UPA treatment in the
36 current scenario was measured as the difference in the number of surgical procedures
37 performed in the current and counterfactual scenarios.
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45 **Historical data on preoperative UPA therapy**

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3 The numbers of UPA treatment units reimbursed¹⁸ in 2013, 2014, 2015 and 2016 were
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5 respectively 5,328, 34,956, 54,076 and 78,762, corresponding to 2,220, 12,227, 18,552 and
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7 26,954 treatment initiations^b.
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10 For subsequent years, it was assumed that market penetration would be maximal in this
11
12 indication by the end of 2016 (stabilization of the number of treatment initiations in the
13
14 preoperative indication). The extrapolated numbers of treatment units were 80,862 for each
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16 year from 2017 to 2019, corresponding to 26,954 treatment initiations per year. In other
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18 words, we extrapolated that about 70% of scheduled surgeries between 2016 and 2019 would
19
20 be preceded by UPA treatment.
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23 **Exploratory scenario with the intermittent UPA indication**

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25 The dose regimen considered for intermittent treatment in this analysis was that used in the
26
27 PEARL IV trial, i.e. four 3-month courses separated by a drug-free period until the start of the
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29 second menstrual period after the end of the previous course (approximately 2 months),
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31 with 3 months of follow-up after the 4th course (total study duration 21 months). The impact
32
33 of intermittent indication on surgical procedures depends mainly on the age at which UPA
34
35 treatment starts. When prescribed to a woman nearing the menopause, UPA could suppress
36
37 symptoms and result in postponement of surgery until beyond the menopause, when it would
38
39 no longer be necessary for most women. Under these assumptions, UPA can be considered a
40
41 relevant alternative to surgery.
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47 Within this framework, the budget impact of the intermittent indication in the study
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49 population was estimated under the assumption that UPA would be prescribed first to women
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55 ^b The estimation of the number of treatment initiations was based on the following hypotheses: 1) all treatment units were sold for the
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57 preoperative indication; 2) each patient took 3 treatment units; and 3) treatment initiations were smoothed over time.
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3 nearing the menopause (≥ 48 years old) during the period 2017 to 2019, with the objective of
4
5 avoiding surgery.
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8 In this scenario, as the aim of intermittent treatment is to avoid surgery and, consequently,
9
10 preoperative treatment, the benefits of preoperative treatment were estimated after taking into
11
12 account surgical procedures avoided through the use of intermittent treatment. Thus, this
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14 exploratory analysis was modeled on the estimated number of surgical procedures in the
15
16 counterfactual scenario.
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19 Starting with the number of surgical procedures that would be done if UPA was not
20
21 available^c, we estimated that:
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24 • 31% of these procedures would have involved women ≥ 48 years old (analysis of the
25
26 PMSI database showed that age at surgery was stable over time – **Figure 2**);
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- 28
29 • Respectively 20%, 40% and 60% of the surgeries warranted for women ≥ 48 years old in
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31 2017, 2018 and 2019 would have been avoided thanks to intermittent UPA treatment,
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33 assuming market penetration similar to that observed for preoperative UPA during the
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35 first 3 years on the French market.
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39 On this basis, the estimated numbers of women who would be prescribed intermittent
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41 treatment were 2,348 in 2017, 4,712 in 2018 and 7,093 in 2019.
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44 By smoothing those initiations uniformly over the year, the estimated numbers of treatment
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46 units reimbursed for intermittent treatment were 10,566 in 2017, 36,466 in 2018 and 64,895 in
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48 2019.
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56 ^c Number of surgeries estimated in the counterfactual scenario, assuming the non use of UPA: 37 466 in 2017, 37 598 in 2018 and 37
57 729 in 2019.
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3 The annual number of surgical procedures would be reduced by the number of intermittent
4 treatment initiations. At the end of intermittent UPA treatment, surgery was only supposed to
5 proceed when the menopause did not occur during the treatment sequence. The probability
6 that the menopause would occur during intermittent UPA treatment was estimated at 59%
7 among women ≥ 48 years old, based on information provided by the French National
8 Authority for Health (*Haute Autorité de Santé*; HAS)¹⁹. Further details about the estimation of
9 the probability of occurrence of menopause are provided in **Appendix**.

10
11
12 Taking into account intermittent treatment initiations, the resulting deferral of surgery, and the
13 cancellation of surgery in 59% of cases at the end of UPA treatment, we estimated that
14 respectively 35,118, 33,129 and 31,851 women would be scheduled for UF surgery in 2017,
15 2018 and 2019. A graphical representation of the calculation is shown in **Figure 3**.

16
17
18 Finally, the subsequent impact of preoperative treatment was modeled in women eligible for
19 surgery who did not start intermittent treatment during the study period^d. Based on the
20 proportion of surgeries preceded by preoperative treatment, and the proportion of surgeries
21 avoided after preoperative treatment in the current scenario, we estimated that respectively
22 25,265, 23,576 and 21,887 women would be prescribed preoperative treatment, resulting in
23 4,191, 3,911 and 3,631 surgeries avoided in 2017, 2018 and 2019, respectively. The estimated
24 numbers of treatment units reimbursed for this indication in the exploratory scenario were
25 76,217 in 2017, 71,150 in 2018 and 66,083 in 2019.

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28 By jointly considering the outcomes measured in both indications, the estimated number of
29 surgical procedures in the exploratory scenario was 30,927 in 2017, 29,218 in 2018 and
30 2019.

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56 ^d 35 118 in 2017, 32 886 in 2018, and 30 636 in 2019.
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3 28,220 in 2019, with respectively 86,783, 107,616 and 130,978 UPA treatment units
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5 reimbursed over this period.

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8 The number of surgical procedures avoided by the use of UPA in both its indications was
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10 estimated in the exploratory scenario as the difference in the number of surgical procedures
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12 performed between the exploratory and counterfactual scenarios.
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14 **Cost of surgical procedures**

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16 For public hospitals, the costs of surgical procedures were calculated from 2015 public DRG
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18 tariffs.²⁰ Private hospitals use the 2015 private DRG tariffs²⁰, to which physician's fees were
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20 added²¹, as they are not included in private DRG tariffs and are reimbursed on a fee-for-
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22 service basis. The estimated average cost of a surgical procedure for uterine fibroids was
23
24 2,416 € (SD=1,126). Surgical procedures are fully reimbursed by the French national
25
26 healthcare insurance system.
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30 Detailed costs are shown in **Table 3** according to the type of surgery and route.
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33 **Assessment of the budget impact**

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35 The costs and benefits resulting each year from the current and exploratory scenarios were
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37 computed by taking the following steps:
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41 • The costs avoided through lesser use of surgery were estimated by multiplying the number
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43 of surgical procedures avoided in the relevant scenario by the total average cost of one
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45 surgical procedure;
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49 • The amount reimbursed to patients by the French national healthcare insurance system for
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51 the use of UPA in the relevant scenario was estimated from the annual number of
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53 reimbursed treatment units in the relevant scenario, the public price of UPA, and a 65%
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55 patient reimbursement rate.
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3 Finally, the budget impact in each scenario was calculated as the difference between the
4 amount reimbursed for UPA by the French national healthcare insurance system in the
5 relevant scenario and the costs avoided through lesser use of surgery.
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9 10 **Sensitivity analyses**

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12 The sensitivity of the cumulative budget impact from 2013 to 2019 for each indication
13 (preoperative and intermittent use) to the principal parameters was assessed in deterministic
14 sensitivity analyses, in which each of the following parameters was varied individually:
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20 • Number of surgical procedures: the bounds of the 95 percent confidence intervals for
21 regression coefficients used to extrapolate the number of surgical procedures with and
22 without preoperative UPA were used to derive potential worst-case and best-case
23 scenarios for UPA. In the best-case scenario, the trend without UPA was maximized
24 (+177 surgical procedures per year) and the trend with UPA was minimized (-1,207
25 surgical procedures per year). In the worst-case scenario, the trend without UPA was
26 minimized (+86 surgical procedures per year) and the trend with UPA was maximized (-
27 1,057 surgical procedures per year);
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- 38 • Budget impact from the societal perspective: each year, a study organized by the French
39 Agency for Information on Hospital Care (*Agence Technique de l'Information sur*
40 *l'Hospitalisation*; ATIH) estimates the costs associated with hospital stays from a societal
41 perspective, using an analytical accounting system in a sample of French hospitals.²²
42
43 Using data from this study, we estimated that the total average cost of a surgical procedure
44 was 2,810 €. In keeping with the societal perspective, the hospital per diem charges,
45 which are supported by the patient, were added to the total cost of the surgical procedure.
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60 Those charges depend on the length of the hospital stay and were estimated at 72 €. In this

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3 analysis, total UPA treatment costs were considered, rather than the portion reimbursed by
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5 CNAM;

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8 • Indirect costs associated with sick leave: one particularity of the French national
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10 healthcare system is partial compensation for sick leave. The national database
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12 (DAMIR)²³ gathering all expenditures of the French national healthcare insurance system
13
14 allowed us to estimate the average daily compensation for sick leave at 31 €. By taking
15
16 into account an average 30-day period of sick leave after UF surgery²⁴ and an employment
17
18 rate of 92% among women with uterine fibroids²⁵, the average cost of sick leave after UF
19
20 surgery was estimated at 856 €;
- 21
22
23 • Duration of exposure during intermittent treatment: based on the PEARL II results
24
25 showing a maintenance of the effect of UPA on UF size and no return to initial symptoms
26
27 severity scores 6 months after treatment, and on PREMYA²⁶ results confirming the
28
29 satisfaction of both patients and healthcare professionals at least 6 months after treatment
30
31 cessation, the off-treatment periods and the follow-up period were both extended to 6
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33 months. The total duration of UPA exposure during intermittent treatment was therefore
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35 expanded to 36 months. This assumption has an impact on the probability of menopause
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37 occurring during intermittent treatment and the age at which intermittent treatment can be
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39 prescribed with the objective of avoiding surgery. Accordingly, intermittent treatment was
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41 supposed to be prescribed in women ≥ 47 years old in this analysis.
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RESULTS

Current scenario

From 2013 to 2015, 94,360 UPA treatment units were reimbursed by the French national healthcare insurance system for the preoperative indication, costing 8.7 M€. Over the same period, use of UPA was associated with 5,645 fewer surgeries. The resulting cost saving was estimated at 13.6 M€.

From 2016 to 2019, the number of UPA treatment units reimbursed by the French national healthcare insurance system for the preoperative indication was extrapolated to 321,348 units, for a cost of 29.7 M€. Over the same period, extrapolation suggested 17,885 fewer surgeries, saving 43.2 M€.

Finally, the estimated cumulative budget impact of preoperative UPA from 2013 to 2019 was -18.5 M€. Detailed annual results are shown in **Table 4**. The number of surgeries performed in each scenario is shown on a larger timeframe in **Figure 1**.

Exploratory scenario

From 2013 to 2016, the exploratory and current scenarios produced the same outcomes, with an estimated cumulative UPA budget impact of -8.5 M€ over the period.

From 2017 to 2019, by comparison with the current scenario, the arrival of intermittent UPA treatment in the exploratory scenario was associated with an increase in the number of reimbursed treatment units and in the number of surgical procedures avoided. With 325,377 treatment units reimbursed from 2017 to 2019 in the exploratory scenario, we estimate that treatment costs in the study population would increase by 34.1% after the arrival of intermittent UPA, cumulating at 30.1 M€ over the period. On the other hand, we estimated that the number of surgical procedures avoided from 2017 to 2019 would increase by 82.1%

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3 after the arrival of intermittent UPA, resulting in a cost saving of 59.0 M€ over the period.
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5 Overall, the cumulative budget impact of UPA from 2017 to 2019 in this scenario was
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7 estimated at -28.9 M€.
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10 Finally, the cumulative budget impact of UPA in both indications from 2013 to 2019 was
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12 estimated at -37.4 M€. Detailed annual results are shown in **Table 5**. The number of surgeries
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14 performed in each scenario is shown on a larger timeframe in **Figure 1**.
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17 Over the studied time horizon, the economic benefit of UPA is due jointly to the increasing
18
19 market penetration of intermittent treatment and to the deferral of surgery. Over the long term,
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21 when prescriptions for intermittent treatment have stabilized, the economic benefits
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23 associated with the intermittent indication will be entirely driven by the number of surgeries
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25 that are cancelled because of menopause occurrence. However, with an average 59%
26
27 probability of menopause occurrence during intermittent treatment, UPA is still expected to
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29 save costs for the French national healthcare insurance system over the long term, when
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31 prescribed to women ≥ 48 years old.
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35 **Sensitivity analyses**

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37 The results were mostly sensitive to the extrapolation of the number of surgical procedures,
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39 the perspective, and surgical costs (**Table 6**). However, the use of UPA was always associated
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41 with considerable savings for the French national healthcare insurance system in both
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43 scenarios.
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DISCUSSION

This study based on observational retrospective data shows that the use of UPA in its first, preoperative indication resulted in substantial cost savings (5.0 M€) for the French national healthcare insurance system from 2013 to 2015. The corresponding savings extrapolated from 2016 to 2019 were 13.5 M€. The incremental benefits associated with the intermittent treatment indication were estimated at 19.0 M€ from 2017 to 2019. However, the economic benefits of intermittent treatment are likely to decrease over time, due to stabilization of prescriptions and to a lesser impact of temporary deferral of surgery. Even in the long term, intermittent treatment is expected to save costs for the French national healthcare insurance system in the study population by offering a curative medical option for perimenopausal women.

There are no comparable pharmacoeconomic evaluations of UPA in the literature. An Italian study²⁷ compared intermittent use to preoperative use, estimating the incremental cost-effectiveness ratio (ICER) between the two strategies and the budget impact of intermittent treatment. The authors concluded that, compared to former preoperative use, intermittent UPA therapy had a favorable pharmacoeconomic profile and was cost-saving for the national healthcare system. Our results are consistent with these findings, as we found that intermittent treatment was associated with more substantial benefits than preoperative treatment in comparable marketing conditions.

The budget impact of the preoperative indication reported here is based on real-world data recorded in France at the national level and on conservative economic assumptions. During the observation period, no other explanation was found for the inflexion point noted when UPA was first marketed, especially as both events (inflexion point and launch of UPA) were simultaneous and proportional (the estimated proportion of surgeries avoided per initiation to

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3 preoperative treatment was stable over time, i.e. 15.8% in 2014, 16.1% in 2015 and 16,6% in
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5 2016). Extrapolation of the economic benefit of this first indication to future years was less
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7 factual, but we adopted a conservative approach by assuming that prescriptions would reach a
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9 plateau.

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12 More assumptions were used for the exploratory scenario, and the estimates are therefore less
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14 robust. However, the economic benefits associated with surgery avoidance through the use of
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16 intermittent treatment depended on the probability of menopause occurring during the UPA
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18 treatment sequence. The results of the PEARL II study, confirmed by real-world data in the
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20 PREMYA study²⁶, suggest that this approach is conservative, as efficacy and satisfaction
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22 persisted at least during a 6-month follow-up period.
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26 In routine practice, the precise level of cost savings will depend on effective UPA usage by
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28 physicians, and on the ability to adjust the dose regimen to the individual patient. Also, some
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30 patients could be treated for longer than expected, depending on symptoms occurrence and
31
32 the wish of the patient to avoid or postpone surgery.
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36 The present evaluation was limited to a portion of the therapeutic area targeted by intermittent
37
38 treatment. As UPA can control UF symptoms for long periods, intermittent treatment is likely
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40 to be increasingly prescribed to women with less severe symptoms and to younger patients
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42 with childbearing potential.
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46 Too little real-world information is available to address the use of intermittent UPA in routine
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48 practice, whereas the impact of preoperative treatment on the use of surgery has been robustly
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50 quantified. Analyses of intermittent UPA treatment based on French medical-administrative
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52 databases will help answer this question.
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TABLES

Table 1. CCAM codes used to identify surgical procedures within the PMSI.

Access route	Hysterectomy	Myomectomy	Embolization
Vaginal	JKFA005; JKFA026		
Laparoscopy	JKFA006; JKFA018 JKFC002; JKFC005 JKFC006	JKFC001; JKFC004	
Laparotomy	JKFA015; JKFA024 JKFA028; JKFA032	JKFA016; JKFA022	
Hysteroscopy		JKFE002	
Intra-arterial			EDSF004; EDSF014

Table 2. Numbers of surgical procedures in the counterfactual and current scenarios.

	2013	2014	2015	2016	2017	2018	2019
Counterfactual scenario without UPA	36,940*	37,071*	37,203*	37,335*	37,466*	37,598*	37,729*
Current scenario with preoperative UPA	36,216	35,129	34,224	32,863*	32,995*	33,127*	33,258*

*Extrapolated data

Table 3. Average cost of surgical procedures according to the type of surgery and route in 2015.

Access route	Hysterectomy	Myomectomy	Embolization
Vaginal	2,975 € (N = 4,966)		
Laparoscopy	3,040 € (N = 5,476)	2,434 € (N = 1,706)	
Laparotomy	3,283 € (N = 7,566)	2,604 € (N = 3,523)	
Hysteroscopy		1,154 € (N = 10,333)	
Intra-arterial			1,786 € (N = 654)

Table 4. Budget impact of preoperative UPA treatment in the current scenario.

	2013	2014	2015	2016	2017	2018	2019
Treatment costs resulting from the use of UPA							
Number of reimbursed treatment units	5,328	34,956	54,076	78,762	80,862	80,862	80,862
Amount reimbursed by the French national healthcare insurance system (M€)	0.5	3.2	5.0	7.3	7.5	7.5	7.5
Surgical procedures avoided by the use of UPA							
Number of surgical procedures avoided	724	1,942	2,979	4,472	4,471	4,471	4,471
Cost saving (M€)	1.7	4.7	7.2	10.8	10.8	10.8	10.8
Budget impact of UPA							
Annual (M€)	-1.3	-1.5	-2.2	-3.5	-3.3	-3.3	-3.3
Cumulative (M€)	-1.3	-2.7	-5.0	-8.5	-11.8	-15.1	-18.5

Table 5. Budget impact of preoperative and intermittent UPA in the exploratory scenario.

	2013	2014	2015	2016	2017	2018	2019
Cost of UPA							
Number of reimbursed treatment units	5,328	34,956	54,076	78,762	86,783	107,616	130,978
Amount reimbursed by the French national healthcare insurance system (M€)	0.5	3.2	5.0	7.3	8.0	9.9	12.1
Surgical procedures avoided by the use of UPA							
Number of surgical procedures avoided	724	1,942	2,979	4,472	6,539	8,380	9,509
Costs avoided (M€)	1.7	4.7	7.2	10.8	15.8	20.2	23.0
Budget impact of UPA							
Annual (M€)	-1.3	-1.5	-2.2	-3.5	-7.8	-10.3	-10.9
Cumulative (M€)	-1.3	-2.7	-5.0	-8.5	-16.3	-26.6	-37.4

Table 6. Sensitivity of the cumulative budget impact (M€) of UPA to the principal parameters from 2013 to 2019, in its two indications.

Scenario	Current scenario: Preoperative use only	Exploratory scenario: Both indications available
Reference analysis	-18.5	-37.4
Worst-case extrapolation of the number of surgeries	-2.7	-22.5
Best-case extrapolation of the number of surgeries	-34.3	-52.4
Budgetary impact from societal perspective	-8.8	-28.7
Indirect costs associated with sick leave	-38.6	-67.0
36-month intermittent treatment period	-18.5	-48.5

FIGURES

Figure 1. Assessment of the impact of UPA on the number of surgical procedures for uterine fibroids in both scenarios.

Figure 2. Age at surgery over time.

Figure 3. Calculation of the number of surgical procedures scheduled from 2017 to 2019, after taking into account the impact of intermittent UPA treatment.

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APPENDIX

Age at surgery

The data retrieved from the PMSI (**Figure 2**) show that the repartition of the age at surgery was stable over time, with more than 90% of the women being aged between 30 and 60 years old. This repartition was unaffected by the arrival of UPA in August 2013.

Severity index of hospital stays with surgery for UF

In France, the severity index of the hospital stay is identified by the 6th letter of the DRG, and can be designated by a number (from least to most severe: 1, 2, 3, 4) or a letter (“J” for outpatient stays, “T” for short-term medical stays and “Z” for stays which are not associated to any severity index, such as chemotherapy sessions).

The severity indexes associated to the surgical procedures realized each year are presented below:

Year	Severity index							TOTAL
	1	2	3	4	J	T	Z	
2008	27,323 (75,2%)	1,712 (4,7%)	254 (0,7%)	55 (0,2%)	261 (0,7%)	43 (0,1%)	6,683 (18,4%)	36,331
2009	25,896 (71,6%)	2,245 (6,2%)	321 (0,9%)	57 (0,2%)	333 (0,9%)	52 (0,1%)	7,257 (20,1%)	36,161
2010	25,148 (69,9%)	2,387 (6,6%)	379 (1,1%)	81 (0,2%)	344 (1,0%)	53 (0,1%)	7,591 (21,1%)	35,983
2011	25,065 (67,8%)	2,481 (6,7%)	392 (1,1%)	70 (0,2%)	437 (1,2%)	59 (0,2%)	8,438 (22,8%)	36,942
2012	24,907 (67,1%)	2,316 (6,2%)	525 (1,4%)	90 (0,2%)	421 (1,1%)	46 (0,1%)	8,841 (23,8%)	37,146
2013	23,836 (65,8%)	2,388 (6,6%)	511 (1,4%)	66 (0,2%)	408 (1,1%)	67 (0,2%)	8,940 (24,7%)	36,216
2014	22,628 (64,4%)	2,416 (6,9%)	453 (1,3%)	77 (0,2%)	470 (1,3%)	67 (0,2%)	9,018 (25,7%)	35,129
2015	21,543 (62,9%)	2,395 (7,0%)	495 (1,4%)	86 (0,3%)	523 (1,5%)	60 (0,2%)	9,122 (26,7%)	34,224

As the French DRG system was restructured in 2008, the hospital stays occurring during the previous years (2006 and 2007) could not be compared in terms of severity indexes and were not presented above.

These data show a regular decrease (resp. increase) in the number of hospital stays associated to the severity index “1” (resp. “Z”) over time. The other severity indexes remained uncommon (approximately 10% of the stays in 2015). These trends were unaffected by the arrival of UPA in August 2013.

Type of surgery realized for UF

The type of surgical procedures realized each year is presented below:

Year	Hysterectomy	Myomectomy	Embolization	Total
2006	21,799 (62,1%)	12,785 (36,4%)	537 (1,5%)	35,121
2007	22,516 (60,9%)	13,818 (37,4%)	630 (1,7%)	36,964
2008	21,386 (58,9%)	14,200 (39,1%)	745 (2,1%)	36,331
2009	20,733 (57,3%)	14,715 (40,7%)	713 (2,0%)	36,161
2010	20,620 (57,3%)	14,605 (40,6%)	758 (2,1%)	35,983
2011	20,675 (56,0%)	15,425 (41,8%)	842 (2,3%)	36,942
2012	20,318 (54,7%)	16,022 (43,1%)	806 (2,2%)	37,146
2013	19,483 (53,8%)	15,846 (43,8%)	887 (2,4%)	36,216
2014	18,837 (53,6%)	15,579 (44,3%)	713 (2,0%)	35,129
2015	18,008 (52,6%)	15,562 (45,5%)	654 (1,9%)	34,224

These data show a regular decrease (resp. increase) in the use of hysterectomy (resp. myomectomy) over time. These trends were unaffected by the arrival of UPA in August 2013.

Extrapolation of the number of hospital stays with surgery for UF

The numbers of surgical procedures realized each month are presented below:

Year	Month	Flag	Number of surgeries (within the month)	Number of surgeries (year-to-date)
2006	1	1	3,218	
2006	2	2	3,104	
2006	3	3	3,275	
2006	4	4	3,130	
2006	5	5	2,846	
2006	6	6	3,238	
2006	7	7	2,668	
2006	8	8	1,457	
2006	9	9	2,942	
2006	10	10	3,463	
2006	11	11	3,071	
2006	12	12	2,709	
2007	1	13	3,214	35,117
2007	2	14	3,238	35,251
2007	3	15	3,522	35,498
2007	4	16	3,091	35,459
2007	5	17	2,801	35,414
2007	6	18	3,525	35,701
2007	7	19	3,008	36,041
2007	8	20	1,619	36,203
2007	9	21	3,153	36,414
2007	10	22	3,731	36,682
2007	11	23	3,244	36,855
2007	12	24	2,818	36,964
2008	1	25	3,090	36,840
2008	2	26	3,219	36,821
2008	3	27	3,261	36,560
2008	4	28	3,315	36,784

2008	5	29	2,934	36,917
2008	6	30	3,426	36,818
2008	7	31	2,894	36,704
2008	8	32	1,626	36,711
2008	9	33	3,166	36,724
2008	10	34	3,491	36,484
2008	11	35	3,181	36,421
2008	12	36	2,728	36,331
2009	1	37	3,121	36,362
2009	2	38	3,094	36,237
2009	3	39	3,529	36,505
2009	4	40	3,101	36,291
2009	5	41	3,035	36,392
2009	6	42	3,350	36,316
2009	7	43	2,755	36,177
2009	8	44	1,697	36,248
2009	9	45	2,970	36,052
2009	10	46	3,618	36,179
2009	11	47	3,211	36,209
2009	12	48	2,680	36,161
2010	1	49	3,244	36,284
2010	2	50	3,078	36,268
2010	3	51	3,351	36,090
2010	4	52	2,916	35,905
2010	5	53	3,047	35,917
2010	6	54	3,374	35,941
2010	7	55	2,827	36,013
2010	8	56	1,756	36,072
2010	9	57	2,944	36,046
2010	10	58	3,604	36,032
2010	11	59	3,143	35,964
2010	12	60	2,699	35,983
2011	1	61	3,497	36,236
2011	2	62	3,224	36,382
2011	3	63	3,337	36,368
2011	4	64	3,192	36,644
2011	5	65	3,412	37,009
2011	6	66	3,028	36,663
2011	7	67	2,713	36,549
2011	8	68	1,757	36,550
2011	9	69	3,099	36,705
2011	10	70	3,599	36,700
2011	11	71	3,321	36,878
2011	12	72	2,763	36,942
2012	1	73	3,429	36,874
2012	2	74	3,285	36,935
2012	3	75	3,453	37,051
2012	4	76	3,137	36,996
2012	5	77	2,784	36,368
2012	6	78	3,507	36,847
2012	7	79	2,938	37,072
2012	8	80	1,750	37,065
2012	9	81	3,085	37,051
2012	10	82	3,691	37,143
2012	11	83	3,245	37,067
2012	12	84	2,842	37,146
2013	1	85	3,286	37,003
2013	2	86	3,160	36,878
2013	3	87	3,324	36,749
2013	4	88	3,169	36,781
2013	5	89	2,753	36,750
2013	6	90	3,363	36,606
2013	7	91	3,080	36,748
2013	8	92	1,684	36,682
2013	9	93	3,068	36,665

2013	10	94	3,495	36,469
2013	11	95	3,157	36,381
2013	12	96	2,677	36,216
2014	1	97	3,168	36,098
2014	2	98	3,261	36,199
2014	3	99	3,243	36,118
2014	4	100	3,000	35,949
2014	5	101	2,937	36,133
2014	6	102	2,960	35,730
2014	7	103	2,731	35,381
2014	8	104	1,615	35,312
2014	9	105	2,979	35,223
2014	10	106	3,418	35,146
2014	11	107	3,180	35,169
2014	12	108	2,637	35,129
2015	1	109	3,016	34,977
2015	2	110	3,046	34,762
2015	3	111	3,129	34,648
2015	4	112	3,015	34,663
2015	5	113	2,730	34,456
2015	6	114	3,122	34,618
2015	7	115	2,603	34,490
2015	8	116	1,593	34,468
2015	9	117	2,850	34,339
2015	10	118	3,385	34,306
2015	11	119	3,093	34,219
2015	12	120	2,642	34,224

Two linear regressions were performed on this dataset:

- Before the arrival of UPA : from flag 13 to flag 91;
- After the arrival of UPA: from flag 92 to flag 120.

The following regression equation was estimated:

$$N(f) = \alpha + \beta * f + \varepsilon$$

With:

- f , the flag associated to the considered month, i.e. regressor;
- $N(f)$, the number of surgeries realized (year-to-date) at the considered flag, i.e. dependent variable;
- α , the independent term of the linear model, i.e. intercept;
- β , the monthly trend in the number of surgeries (year-to-date), i.e. regression coefficient;
- ε , the unobserved random noise, i.e. residuals.

The results of the parameter estimation procedure are presented below:

	Intercept	Regression coefficient (SE)	R-squared
Before UPA	35,886.8	+10.97 (1.94)	0.29

After UPA	45,316.1	-94.34 (3.19)	0.97
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The trends before UPA and after UPA were respectively extrapolated from flag 92 and 121, using the regression equation ($\mathbb{N}(f) = \alpha + \beta * f$) estimated above.

Estimation of the probability of occurrence of menopause

The probability that the menopause would occur during intermittent UPA treatment was based on information provided by the French National Authority for Health (*Haute Autorité de Santé*; HAS)¹⁹, which reports that respectively 7%, 33% and 83% of women in the 40-44, 45-49 and 50-54 year age groups are postmenopausal. Nearly all French women over 60 years of age are postmenopausal.

In order to estimate the probability for each surgical procedure to be postponed beyond menopause, a beta distribution has been matched on the proportions presented by the HAS. The support of the distribution was defined between 30 and 60. The shape parameters α and β were estimated at 10.47 and 6.00, respectively. The proportion of postmenopausal women was calibrated at 5% between 40 and 44, 33% between 45 and 49, and 81% between 50 and 54.

The probability \mathbb{P}_R for each surgical procedure to be postponed beyond menopause was calculated according to the following formulae:

$$\mathbb{P}_R(A, E) = \mathbb{P}(X - A \leq E \mid X > A) = 1 - \mathbb{P}(X - A > E \mid X > A) = 1 - \frac{\mathbb{S}(A + E)}{\mathbb{S}(A)}$$

With:

- X, a random variable following the beta distribution estimated above;
- $\mathbb{S}(\cdot)$, the survival function associated to the beta distribution estimated above;
- A, the age of the women undergoing surgical procedure;
- E, the duration of exposure considered for intermittent treatment (21 or 42 months);

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- $\mathbb{P}_R(A, E)$, the probability for a women, which is not postmenopausal at the age A, to be postmenopausal at the age A+E.

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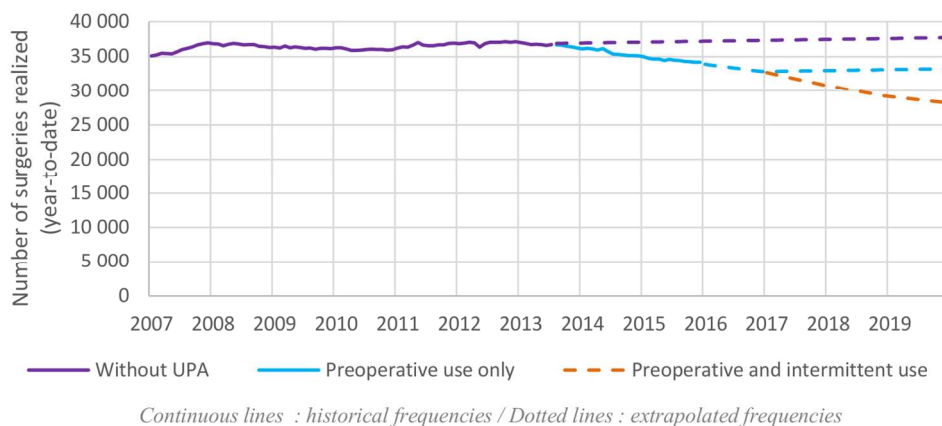
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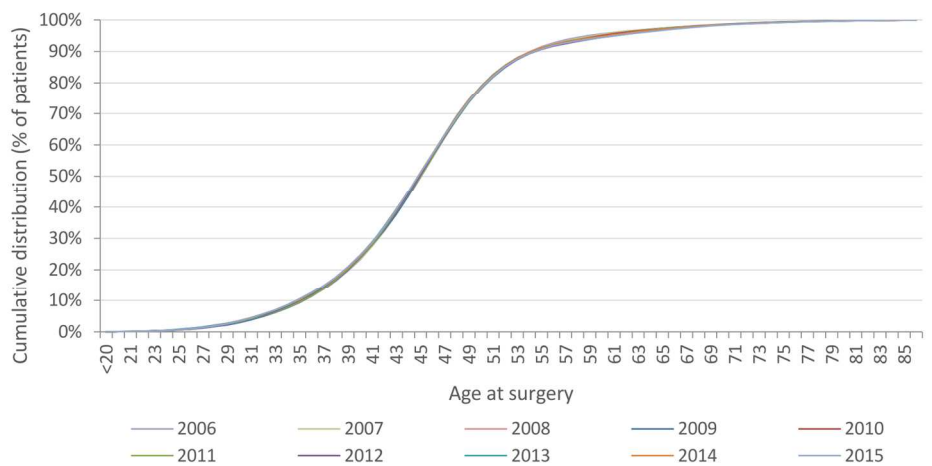
Assessment of the impact of UPA on the number of surgical procedures for uterine fibroids in both scenarios

173x75mm (300 x 300 DPI)

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Age at surgery over time

173x84mm (300 x 300 DPI)

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35,118 surgeries scheduled in 2017	33,129 surgeries scheduled in 2018	31,851 surgeries scheduled in 2019
=	=	=
37,466 surgeries done without UPA in 2017	37,598 surgeries done without UPA in 2018	37,729 surgeries done without UPA in 2019
-	+	+
2,348 intermittent UPA treatment initiations in 2017	243 surgeries from 2017 deferred to 2018	728 surgeries from 2017 deferred to 2019
$2,348 = 37,466 * P_{age\ group} * 20\%$	$2,348 * 25\%^{[1]} * (1 - P_{menopause})$	$2,348 * 75\%^{[1]} * (1 - P_{menopause})$
	-	+
	4,712 intermittent UPA treatment initiations in 2018	487 surgeries from 2017 deferred to 2018
	$4,712 = 37,598 * P_{age\ group} * 40\%$	$4,712 * 25\%^{[1]} * (1 - P_{menopause})$
		-
		7,093 intermittent UPA treatment initiations in 2019
		$7,093 = 37,729 * P_{age\ group} * 60\%$
<p>$P_{age\ group}$: proportion of surgeries involving women ≥ 48 years old (31%)</p> <p>$P_{menopause}$: probability of menopause occurrence during UPA treatment among women ≥ 48 years old (59%)</p> <p>[1] : smoothing of UPA initiations over the year implies that 25% (resp.75%) of surgeries in year Y are deferred to year Y+1 (resp.Y+2)</p>		

Calculation of the number of surgical procedures scheduled from 2017 to 2019 after taking into account the impact of intermittent UPA treatment

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