

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

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ABSTRACT

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

Design We modelled 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 uterine fibroids.

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 5645 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 million from 2013 to 2015 and €–13.5 million 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 million.

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.

INTRODUCTION

Uterine fibroids (UF), also known as leiomyomas or myomas, are frequent benign smooth muscle tumours 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, dysmenorrhoea and/or anaemia, thereby undermining quality

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 (UPA) is cost-saving), even during sensitivity analysis and considering the worst-case scenario.
- Conservative approach by excluding indirect costs associated with sick leave (which are partially compensated by the French national healthcare system) and by limiting the market penetration of UPA as a presurgical 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 the limited availability of real-world data related to the use of intermittent UPA in routine practice.

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 years) and 8.8% in a 2014 French survey⁴ (diagnosed symptomatic UF in women aged between 30 and 55 years).

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 UF.^{8 9 10 11}

Based on the results of PEARL I and II,^{7 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.¹² Reimbursement status was granted by the French Ministry of Health and Welfare in 2013 for one 3-month treatment course^{13,14}, and UPA started to be marketed for this preoperative indication in August 2013.

In the PEARL II study, about half of the patients treated with either UPA 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 1 month after the last dose of leuprolide acetate, whereas the fibroid volume reduction was maintained at least up to 6 months after the end of treatment in most patients who received UPA.¹⁵

Recently, the PEARL IV study compared 5 and 10 mg doses of UPA administered as repeated intermittent treatment (up to four 3-month courses, with breaks of 2 months, for a total study duration of 21 months). Uterine bleeding was controlled in, respectively, 73.3% and 75.0% of patients in the two groups at the end of the fourth course. After four courses, myoma volume fell by 67.0% in the 5 mg group and by 70.4% in the 10 mg group, a non-statistically significant difference. Efficacy was maintained during the off-treatment periods.¹⁰

Consequently, in April 2015, EMA extended the indications for UPA to cover repeated intermittent treatment courses of 3 months each in adult women of reproductive age with moderate to severe symptoms from UF.¹⁶ However, this indication is not yet reimbursed by the French national healthcare insurance system.

Although clinical data suggest a positive impact of UPA on the need for surgery among women with symptomatic UF, its economic impact has not been documented. The objective of this study was to assess the budget impact of UPA at the level of the French population, from the point of view of the national healthcare insurance system.

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.¹⁷ On the basis of real-world data, we assessed the budget impact of UPA in women with moderate to severe UF 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 UF 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 with 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 with this counterfactual scenario:

1. The current scenario, based on the use of surgery with UPA available in its current marketing situation in France (ie, the preoperative indication since August 2013);
2. An exploratory scenario modelling the potential incremental impact associated with the reimbursement of intermittent UPA after January 2017 concerning surgical treatment.

In this analysis, the benefits of intermittent indication were limited to the possibility of postponement of the surgery after the occurrence of menopause and, consequently, of avoidance of surgery. As the PEARL IV study¹⁰ evaluated the efficacy of intermittent treatment over a 2-year duration of exposure, the impact of intermittent UPA was only assessed in women nearing the menopause (≥ 48 years old).

In all three scenarios, outcomes were estimated from exhaustive real-world data available in French national databases. The perspective was that of the French national healthcare insurance system (Caisse Nationale d'Assurance Maladie; CNAM). Healthcare costs associated with reimbursed UPA treatment units (standard packs of 28 pills) and surgical procedures were considered. A time horizon of 7 years was chosen (2013–2019) in order to assess the impact of both UPA indications on the surgical management of UF, from the market introduction of preoperative treatment to the end of a 3-year period of intermittent treatment availability.

Identification of surgical procedures in national databases

The number of surgical procedures for UF was estimated from the database of the French Medical Information System (Programme de Médicalisation des Systèmes d'Information; PMSI), which covers all French public and private hospitals. All hospital stays in a given year are available in standardised discharge reports and are collected in the PMSI database. This database is primarily used for invoicing purposes through a diagnosis-related group (DRG) system by hospitals to CNAM, but it can also be used to assess the number of patients treated per year for a specific disease and the number of hospital stays per patient. This database is used for epidemiological purposes by several public health organisations, such as the National Cancer Institute (Institut National du Cancer).

Table 1 CCAM codes used to identify surgical procedures within the PMSI (a French national hospital database)

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

Hospital stays for UF were extracted from the PMSI database by using the ICD-10 codes for UF, namely D25 (leiomyoma of uterus); D25.0 (submucous leiomyoma of uterus); D25.1 (intramural leiomyoma of uterus); D25.2 (subserosal leiomyoma of uterus) and D259 (leiomyoma of uterus, unspecified). The surgical procedures were selected from the PMSI by selecting the specific codes of the French procedure classification (Classification Commune des Actes médicaux), as shown in [table 1](#).

Historical data on the use of surgery for UF

The PMSI data revealed two periods with respect to UF surgery ([figure 1](#)):

- ▶ Before the availability of UPA, from January 2007 to August 2013, when the annual number of UF surgeries was tending to rise;
- ▶ After the availability of UPA for preoperative use (August 2013 to 2015), when the annual number of UF surgeries tended to fall.

In contrast, the repartition of the age at surgery and the trends observed in the characteristics of the hospital stays (severity index, type of surgery) were sustained over the whole period (online supplementary appendix).

The inflexion point in the number of surgeries observed at the time of launch of UPA was solely attributed to the efficacy of UPA, as:

- ▶ Both events (inflexion point and launch of UPA) were simultaneous;
- ▶ There was no other emerging healthcare technology or public health decision which could have impacted the management or the incidence of moderate to severe UF in France at this time.

Within this context, two scenarios were compared ([figure 1](#)):

- ▶ The counterfactual scenario, assuming non use of UPA: the trend observed before market release in France was extrapolated from August 2013 to 2019 by using linear regression and data recorded from January 2007 to August 2013 (+132 surgical procedures per year on average).
- ▶ The current scenario, with preoperative use of UPA: the trend in UF surgery after UPA market release in France was extrapolated to 2016 by using linear regression and data collected from August 2013 to the end of 2015 (-1132 surgical procedures per year

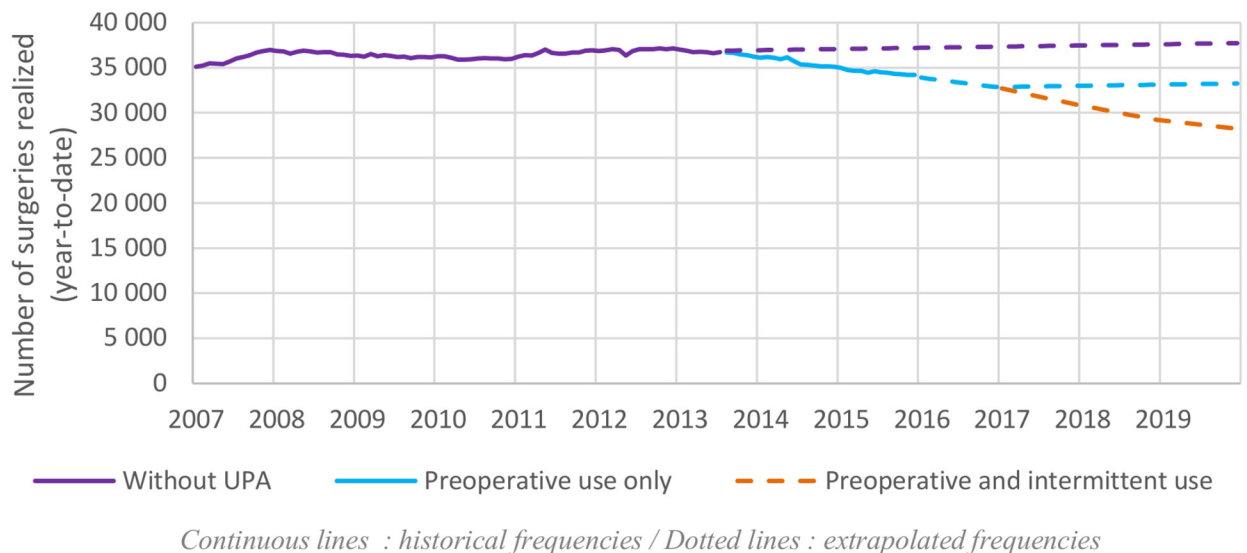

Figure 1 Assessment of the impact of ulipristal acetate (UPA) on the number of surgical procedures for uterine fibroids in both scenarios.

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

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

*Extrapolated data

on average). Adopting a conservative approach, we postulated that market penetration of UPA as a preoperative treatment would reach a plateau at the end of 2016, and that trends in the number of surgical procedures, both with and without preoperative use of UPA, would be identical from that point onwards.

The annual numbers of surgeries performed in the two scenarios over the studied time horizon are shown in [table 2](#). Further details about the linear extrapolation of the number of surgeries (initial data, regression coefficients and extrapolation results) are provided in online supplementary appendix.

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 numbers of UPA treatment units reimbursed¹⁸ in 2013, 2014, 2015 and 2016 were, respectively, 5328, 34 956, 54 076 and 78 762, corresponding to 2220, 12 227, 18 552 and 26 954 treatment initiations¹.

For subsequent years, it was assumed that market penetration would be maximal in this indication by the end of 2016 (stabilisation of the number of treatment initiations in the preoperative indication). The extrapolated numbers of treatment units were 80 862 for each year from 2017 to 2019, corresponding to 26 954 treatment initiations per year. In other words, we extrapolated that about 70% 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, that is, 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 fourth 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 old) during the period 2017–2019, 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 modelled 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,ⁱⁱ we estimated that:

- ▶ About 31% of these procedures would have involved women aged ≥ 48 years (analysis of the PMSI database showed that age at surgery was stable over time—[figure 2](#));
- ▶ Respectively, 20%, 40% and 60% of the surgeries warranted for women aged ≥ 48 years in 2017, 2018 and 2019 would have been avoided thanks to 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, 36 466 in 2018 and 64 895 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

ⁱThe estimation of the number of treatment initiations was 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.

ⁱⁱNumber of surgeries estimated in the counterfactual scenario, assuming the non use of UPA: 37 466 in 2017, 37 598 in 2018 and 37 729 in 2019.

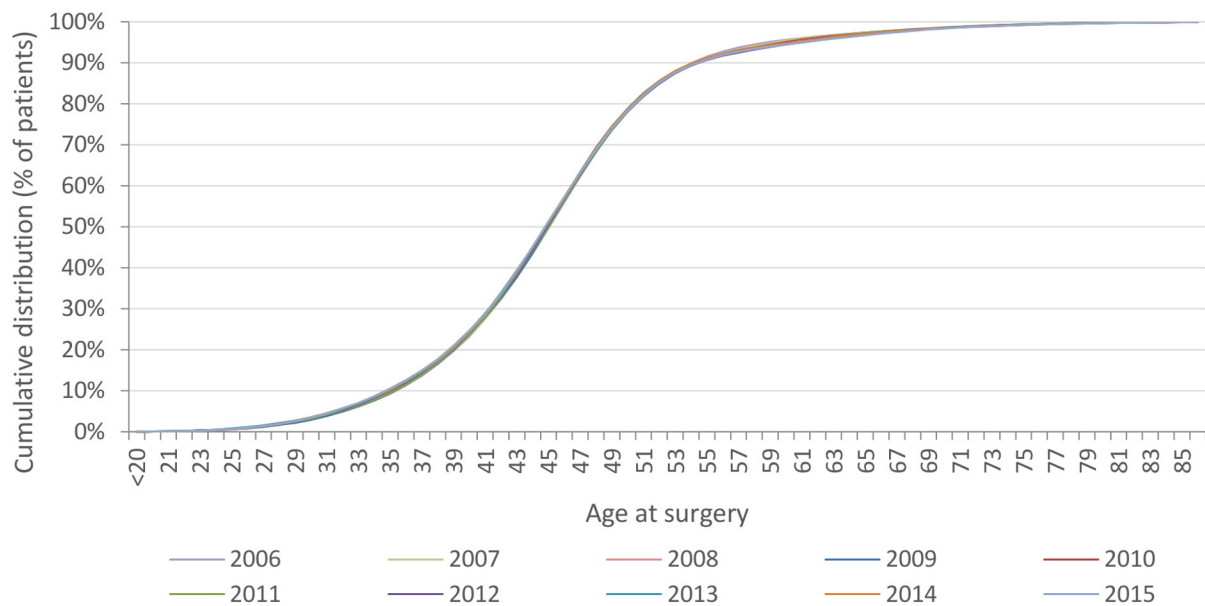


Figure 2 Age at surgery over time.

UPA treatment was estimated at 59% among women aged ≥ 48 years, based on information provided by the French National Authority for Health (Haute Autorité de Santé).¹⁹ Further details about the estimation of the probability of occurrence of menopause are provided in online supplementary appendix.

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 35 118, 33 129 and 31 851 women, respectively, would be scheduled for UF surgery in 2017, 2018 and 2019. A graphical representation of the calculation is shown in figure 3.

Finally, the subsequent impact of preoperative treatment was modelled in women eligible for surgery who did not start intermittent treatment during the study periodⁱⁱⁱ. On the basis of the proportion of surgeries preceded by preoperative treatment and the proportion of surgeries avoided after preoperative treatment in the current scenario, we estimated that 25 265, 23 576 and 21 887 women would be prescribed preoperative treatment, resulting in 4191, 3911 and 3631 surgeries avoided in 2017, 2018 and 2019, respectively. The estimated numbers of treatment units reimbursed for this indication in the exploratory scenario were 76 217 in 2017, 71 150 in 2018 and 66 083 in 2019.

By jointly considering the outcomes measured in both indications, the estimated number of surgical procedures in the exploratory scenario was 30 927 in 2017, 29 218 in 2018 and 28 220 in 2019, with, respectively, 86 783, 107 616 and 130 978 UPA treatment units reimbursed over this period.

ⁱⁱⁱ35 118 in 2017, 32 886 in 2018, and 30 636 in 2019.

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

Cost of surgical procedures

For public hospitals, the costs of surgical procedures were calculated from 2015 public DRG tariffs.²⁰ Private hospitals use the 2015 private DRG tariffs,¹² to which physician's fees were added,²¹ as they are not included in private DRG tariffs and are reimbursed on a fee-for-service basis. The estimated average cost of a surgical procedure for UF was €2416 (SD=1126). Surgical procedures are fully reimbursed by the French national healthcare insurance system.

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 were computed by taking the following steps:

- ▶ The costs avoided through the 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.

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
		$7,093 = 37,729 * P_{age\ group} * 60\%$

$P_{age\ group}$: proportion of surgeries involving women ≥ 48 years old (31%)

$P_{menopause}$: probability of menopause occurrence during UPA treatment among women ≥ 48 years old (59%)

[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)

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

Table 3 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

UPA, ulipristal acetate.

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 the 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% CIs 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 maximised (+177 surgical procedures per year) and the trend with UPA was minimised (-1207 surgical procedures per year). In the worst-case scenario, the trend without UPA was minimised (+86 surgical procedures per year) and the trend with UPA was maximised (-1057 surgical procedures per year);
- ▶ Budget impact from the societal perspective: each year, a study organised by the French Agency for Information on Hospital Care (Agence Technique de l'Information sur l'Hospitalisation) estimates the costs associated with hospital stays from a societal perspective, using an analytical accounting system in a sample of French hospitals.²² Using data from this study, we estimated that the total average cost of a surgical procedure was €2810. In keeping with the societal perspective, the hospital per diem charges, which are supported by the patient, were added to the total cost of the surgical procedure. Those charges depend on the length of the hospital stay and were estimated at €72. In this analysis, total UPA treatment costs were considered, rather than the portion reimbursed by CNAM;
- ▶ Indirect costs associated with sick leave: one particularity of the French national healthcare system is partial compensation for sick leave. The national database (DAMIR)²³ gathering all expenditures of the French national healthcare insurance system allowed us to estimate the average daily compensation for sick leave at €31. By taking into account an

average 30-day period of sick leave after UF surgery²⁴ and an employment rate of 92% among women with UF, (Observational epidemiological study realized by Kantar Health for Gedeon Richter, unpublished data) the average cost of sick leave after UF surgery was estimated at €856;

- ▶ Duration of exposure during intermittent treatment: based on the PEARL II results showing a maintenance of the effect of UPA on UF size and no return to initial symptoms severity scores 6 months after treatment, and on PREMYA²⁵ results confirming the satisfaction of both patients and healthcare professionals at least 6 months after treatment cessation, the off-treatment periods and the follow-up period were both extended to 6 months. The total duration of UPA exposure during intermittent treatment was therefore expanded to 36 months. This assumption has an impact on the probability of menopause occurring during intermittent treatment and the age at which intermittent treatment can be prescribed with the objective of avoiding surgery. Accordingly, intermittent treatment was supposed to be prescribed in women aged ≥47 years in this analysis.

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 million. Over the same period, use of UPA was associated with 5645 fewer surgeries. The resulting cost saving was estimated at €13.6 million.

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 million. Over the same period, extrapolation suggested 17 885 fewer surgeries, saving €43.2 million.

Finally, the estimated cumulative budget impact of preoperative UPA from 2013 to 2019 was €-18.5 million. 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

Access route	Hysterectomy	Myomectomy	Embolisation
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 Average cost of surgical procedures according to the type of surgery and route in 2015

Table 5 Budget impact of preoperative and intermittent ulipristal acetate (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

cumulative UPA budget impact of -€8.5 million 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 million 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% after the arrival of intermittent UPA, resulting in a cost saving of €59 million over the period. Overall, the cumulative budget impact of UPA from 2017 to 2019 in this scenario was estimated at €-28.9 million.

Finally, the cumulative budget impact of UPA in both indications from 2013 to 2019 was estimated at €-37.4 million. Detailed annual results are shown in table 5. The number of surgeries performed in each scenario is shown on a larger timeframe in figure 1.

Over the studied time horizon, the economic benefit of UPA is due jointly to the increasing market penetration of intermittent treatment and to the deferral of surgery. Over the long term, when prescriptions for intermittent treatment

have stabilised, the economic benefits associated with the intermittent indication will be entirely driven by the number of surgeries that are cancelled because of menopause occurrence. However, with an average 59% probability of menopause occurrence during intermittent treatment, UPA is still expected to save costs for the French national healthcare insurance system over the long term, when prescribed to women aged ≥48 years.

Sensitivity analyses

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

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 million) for the French national healthcare insurance system from 2013 to 2015. The corresponding savings extrapolated from 2016 to 2019 were €13.5 million. The incremental benefits associated with the intermittent treatment indication were estimated at €19 million from 2017 to 2019. However, the economic benefits of intermittent treatment

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

UPA, ulipristal acetate.

are likely to decrease over time, due to stabilisation 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 health-care 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 between the two strategies and the budget impact of intermittent treatment. The authors concluded that compared with former preoperative use, intermittent UPA therapy had a favourable 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 preoperative treatment was stable over time, that is, 15.8% in 2014, 16.1% in 2015 and 16.6% in 2016). Extrapolation of the economic benefit of this first indication to future years was less factual, but we adopted a conservative approach by assuming that prescriptions would reach a plateau.

More assumptions were used for the exploratory scenario, and the estimates are, therefore, less robust. However, the economic benefits associated with surgery avoidance through the use of intermittent treatment depended on the probability of menopause occurring during the UPA treatment sequence. The results of the PEARL II study, confirmed by real-world data in the PREMYA study,²⁵ suggest that this approach is conservative, as efficacy and satisfaction persisted at least during a 6-month follow-up period.

In routine practice, the precise level of cost savings will depend on effective UPA usage by physicians, and on the ability to adjust the dose regimen to the individual patient. Also, some patients could be treated for longer than expected, depending on symptoms occurrence and the wish of the patient to avoid or postpone surgery.

The present evaluation was limited to a portion of the therapeutic area targeted by intermittent treatment. As UPA can control UF symptoms for long periods, intermittent treatment is likely to be increasingly prescribed to women with less severe symptoms and to younger patients with childbearing potential.

Too little real-world information is available to address the use of intermittent UPA in routine practice, whereas the impact of preoperative treatment on the use of surgery has been robustly quantified. Analyses of intermittent

UPA treatment based on French medical-administrative databases will help answer this question.

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