

CADTH RAPID RESPONSE REPORT:  
SUMMARY WITH CRITICAL APPRAISAL

# Ulipristal versus Levonorgestrel for Emergency Contraception: A Review of Comparative Cost-Effectiveness

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## Abbreviations

BMI	Body mass index
Cu	Copper
EC	Emergency contraception
ICER	Incremental cost-effectiveness ratio
IUD	Intrauterine device
LNG	Levonorgestrel
UPA	Ulipristal acetate
WTP	Willingness-to-pay

## Context and Policy Issues

A 2016 national online survey conducted by the Society of Obstetricians and Gynecologists in Canada to explore the reproductive health behaviors, attitudes, knowledge and belief about contraception revealed that about 61% of Canadian women had an unintended pregnancy.<sup>1</sup> The direct cost associated with unintended pregnancies in Canada was estimated to be over \$320 million each year, 54.7% of which (\$175 million) was attributable to pregnancies in those aged 20 to 29 years.<sup>2</sup>

Emergency contraception (EC), also known as postcoital contraception, can be provided in the form of oral hormonal drugs or devices such as copper intrauterine devices (Cu IUD) as an emergency measure to prevent unintended pregnancy from unprotected intercourse, contraceptive method failure or sexual assault.<sup>3</sup> However, EC drugs or devices are only effective if pregnancy implantation has not occurred.<sup>3</sup> Although Cu IDU is the most effective EC with a failure rate of less than 0.1%,<sup>4</sup> oral drugs remain the preferred EC methods among users due to easy access, lower up-front costs, and less provider-dependency.<sup>5</sup>

The EC oral drug classes, including progestogen (levonorgestrel [LNG]) and progesterone receptor modulator (ulipristal acetate [UPA]), work primarily by inhibiting or delaying ovulation, with minimal postovulatory mechanisms.<sup>5</sup> In Canada, LNG is a non-prescription drug, while UPA is available only by prescription in some jurisdictions.

The findings of a recent systematic review suggest that UPA may be more effective than LNG for EC use.<sup>6</sup> In a subgroup analysis, those with a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> may experience higher risk of pregnancy compared to those with BMI less than 30 kg/m<sup>2</sup> after intake of LNG or UPA, though the effect in UPA did not reach statistical significance.<sup>7</sup> An evidence-based guideline of the Society of Obstetricians and Gynecologists in Canada recognizes that both UPA and LNB are effective up to five days after unprotected sexual intercourse, but recommends that UPA should be the first choice for those with a BMI  $\geq 25$  kg/m<sup>2</sup>, who are seeking oral EC.<sup>8</sup>

A previous CADTH report reviewed the comparative clinical effectiveness and guidelines on the EC use of UPA versus LNG.<sup>9</sup> The aim of this report is to review the comparative cost-effectiveness of those two EC drugs.

## Research Question

What is the comparative cost-effectiveness of ulipristal versus levonorgestrel for use as emergency contraception?

## Key Findings

Two identified economic studies provided evidence that ulipristal was the cost-effective emergency contraception alternative to levonorgestrel. No studies conducted subgroup analysis based on body mass index.

## Methods

### Literature Search Methods

A limited literature search was conducted on key resources including Medline, PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and January 10, 2019.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Those requesting emergency contraception Subgroups of interest: BMI >25; BMI >30
<b>Intervention</b>	Ulipristal acetate (Ella)
<b>Comparator</b>	Levonorgestrel (Plan B)
<b>Outcomes</b>	Cost effectiveness (QALY, ICER)
<b>Study Designs</b>	Economic evaluations

BMI = body mass index; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year

### Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1 and if they were published prior to 2014.

### Critical Appraisal of Individual Studies

The Joanna Briggs Institute critical appraisal checklist for economic evaluations of was used to assess the quality of the economic studies.<sup>10</sup> Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 114 citations were identified in the literature search. Following screening of titles and abstracts, 112 citations were excluded and two potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. After full-text review, two economic studies met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

### Summary of Study Characteristics

The characteristics of the identified economic studies<sup>11,12</sup> are summarized below and are presented in Appendix 2.

One cost-effectiveness study<sup>11</sup> of four EC strategies (i.e., UPA, oral LNG, Cu IUD, and oral LNG plus same-day LNG IUD) was conducted based on the US payer perspective with a time horizon of one year. The other cost-effectiveness study<sup>12</sup> of two EC methods (i.e., UPA and oral LNG) was conducted based on a collective perspective (i.e., cost of healthcare resources used) in France with a time horizon period from unprotected intercourse until the moment termination of pregnancy occurred, or within eight weeks after birth, in the case of pregnancy carried to term.

The US study<sup>11</sup> used a decision analytic model incorporated with a Markov model to examine the cost-effectiveness of EC methods in women of childbearing age (between 20 to 34 years) and regular menstrual cycle presenting to a clinical setting for EC within five days of unprotected sexual intercourse. The French study<sup>12</sup> also used a decision analytic model to examine the cost-effectiveness of UPA and LNG in young women in France (age ranged from 15 to 17 years) seeking EC within 72 hours of unprotected sexual intercourse. In both studies,<sup>11,12</sup> the treatment effect was mean number of unintended pregnancies for each EC method. The effectiveness estimate comparing UPA and LNG was derived from the results of a randomized non-inferiority study and meta-analysis.<sup>13</sup>

The US study<sup>11</sup> considered only direct medical costs (i.e., cost of pregnancy [US\$5,167] and EC costs), which were calculated based on 2017 US currency and were input into the model. The French study<sup>12</sup> considered only direct healthcare costs (based on 2010 euro) that are linked to the use of EC and to termination, or to term delivery after unintended pregnancy. Discount rates were not used in either study,<sup>11,12</sup> as the time horizon was one year or less. Indirect costs, transportation costs, or cost for loss of productivity were not included.<sup>11,12</sup> The primary outcome in both studies was the incremental cost-effectiveness ratio (ICER) (i.e., incremental cost per pregnancy prevented), and deterministic and probabilistic sensitivity analyses were conducted in both studies.<sup>11,12</sup>

The US study<sup>11</sup> stated that “*Support for this project was provided internally*”, while the French study<sup>12</sup> was financially supported by HRA Pharma, a pharmaceutical company manufactured both LNG and UPA. The author was employed by HRA Pharma at the time of the project.

### Summary of Critical Appraisal

The quality assessment of the economic studies are described below and are presented in Appendix 3.

Both studies<sup>11,12</sup> provided appropriate research questions and objectives, a clear description of intervention(s) and comparator(s), the costs and cost-effectiveness outcomes were identified and appeared to be comprehensive and relevant. The clinical effectiveness in both studies was established, and costs and outcomes were valued credibly. A measure of the change in costs and benefits for the intervention and comparator were performed, and sensitivity analyses were conducted to investigate uncertainty. Both studies<sup>11,12</sup> described the study settings adequately, though it is unclear whether results may be generalizable to the Canadian context. Discount rates were not applicable to both studies,<sup>11,12</sup> as a short time horizon of one year or less was used. Both study results<sup>11,12</sup> did not appear to answer all questions that users or decision makers want to know, as they did not provide information regarding cost-effectiveness of the drugs in specific weight classes, and cost difference between drugs in cases of sexual assault and as an EC in general.

### Summary of Findings

The main findings and conclusions of the included economic studies are presented in Appendix 4.

In the US study,<sup>11</sup> only the comparison between UPA and oral LNG is presented here, since the other EC strategies such as Cu IUD and oral LNG + LNG IUD are out of scope for this review. In women aged between 20 to 34 years presenting to a clinical setting to seek EC within five days of unprotected sexual intercourse, UPA was dominant over LNG, with an ICER of -\$3,982 (i.e., UPA costs less and prevented more pregnancies than oral LNG). In one-way sensitivity analysis, the study compared other EC strategies with UPA as reference group. Oral LNG was dominated by UPA for all cases tested. In a separate one-way sensitivity analysis by varying the proportion of obese women, oral LNG remained less cost-effective than UPA regardless of the proportion of obese women. The two-way sensitivity analysis was irrelevant to the current context of the review, as it was performed to examine the effectiveness of varying the costs of Cu IUD and LNG IUD. The probabilistic sensitivity analysis showed that UPA had higher probability of being most cost-effective compared to oral LNG at willingness-to-pay (WTP) from \$0 to \$10,000. The study did not conduct any subgroup analysis on the cost-effectiveness based on BMI. The authors concluded that UPA cost less and was more effective than LNG.

The French study<sup>12</sup> evaluated the cost-effectiveness of UPA versus LNG in women aged between 15 to 17 years. The base case analysis, in which EC intake was within 72 hours after unprotected intercourse, showed that the ICER was 418.00 €, which was lower than the WTP threshold of 1,630.10 € (i.e., cost of unintended pregnancy). In the intake within the 24 hours subgroup, UPA was dominant with an ICER of -649.49 €. One-way sensitivity analysis of the base case (i.e., intake within 72 hours), UPA was dominant at its lower cost of 19.9 €. In one-way sensitivity analysis of the subgroup (i.e., intake within 24 hours), UPA was dominant in five analyses (i.e., cost of UPA, cost of LNG, cost of birth, cost of miscarriage, and cost of termination). For pregnancy outcome, UPA was dominant at high value. The two-way sensitivity analysis, by varying in pregnancy rates of both drugs, showed that UPA remained dominant method in the majority of both base case and subgroup analyses. At a WTP of 1,630.10 €, the probabilistic sensitivity analysis showed that UPA was the preferred method in 76.9% of cases, and it was superior (more cost effective at lower cost) to LNG in 45% of cases. The authors concluded that UPA was a cost-effective alternative to LNG in young women in France.

## Limitations

Several limitations have been identified in both studies. First, the cost-effectiveness analyses did not measure quality of life, a potentially important outcome for persons with unintended pregnancy. Second, the estimation of pregnancy rates and costs of pregnancy may be imprecise, leading to potential overestimate or underestimate the cost-effectiveness of some EC strategies. Third, the analysis in both studies included only direct costs, while indirect costs to the individual and society were not included. Fourth, both studies did not conduct any subgroup analysis based on BMI, as obesity has been shown to impact the effectiveness of both LNG and UPA.<sup>7</sup> Fifth, the impact of BMI on pregnancy complications and costs was not considered in the analysis.

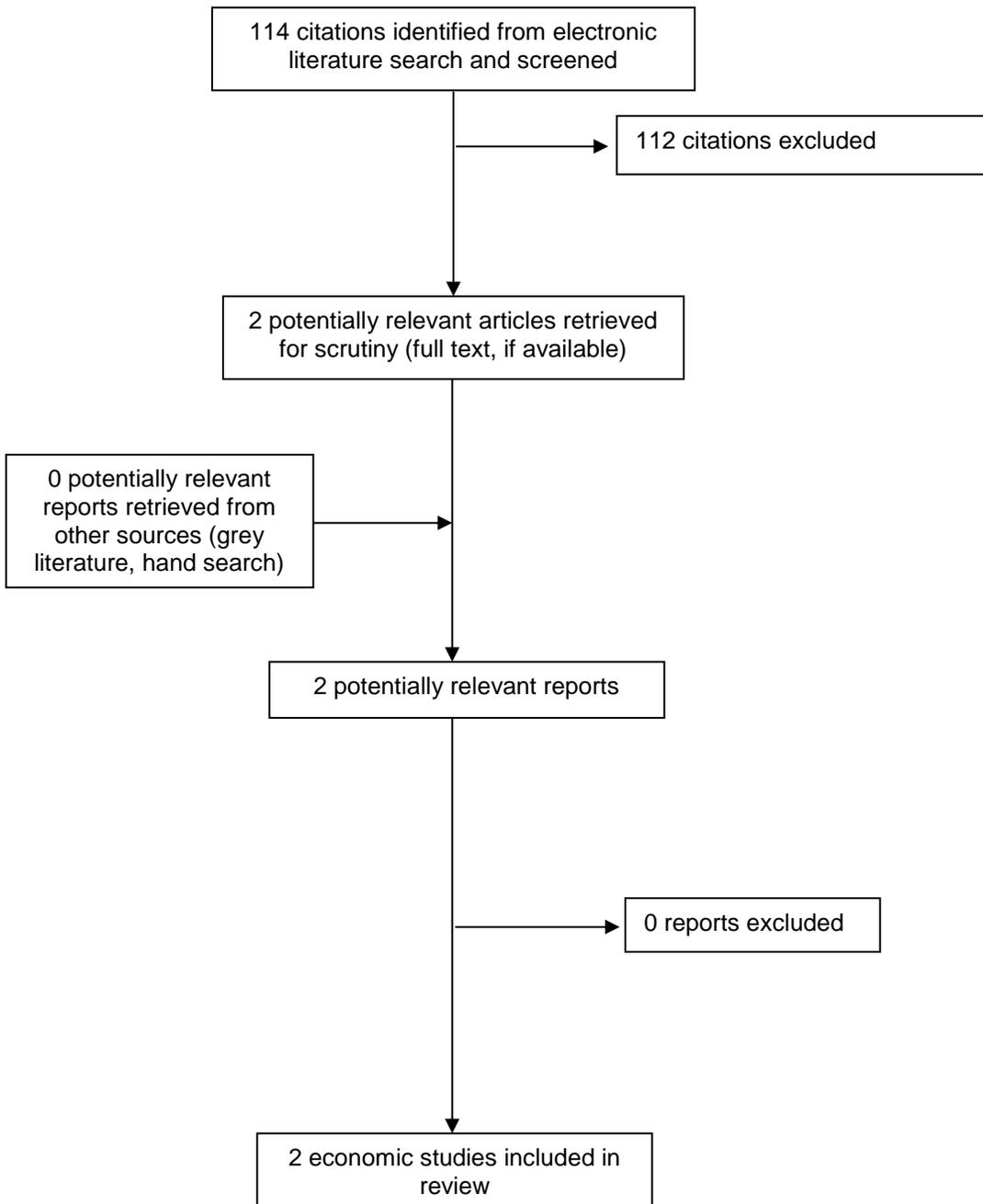
## Conclusions and Implications for Decision or Policy Making

Two economic studies identified in this review provided evidence that UPA was the cost-effective EC alternative to LNG. In the US study,<sup>11</sup> LNG was dominated by UPA, (i.e., UPA cost less and prevented more pregnancies than LNG). Similarly, the French study showed that, among minors in France, UPA dominated LNG when taken within 24 hours of unprotected sexual intercourse. Within 72 hours intake, UPA was a cost-effective alternative to LNG given that the incremental cost per pregnancy prevented with UPA was less than the cost of an unintended pregnancy. Given the identified limitations and the narrow perspectives of the included studies, their findings should be interpreted with caution, as it remains unclear whether they can be generalizable to the Canadian context. Future studies should be conducted to examine the comparative cost-effectiveness of UPA versus LNG for EC use in Canada at a societal perspective with the incorporation of both direct and indirect costs, as well as quality of life. Two cost-effectiveness studies of UPA versus LNG based in the UK and the USA that were published in 2010 and 2013, respectively, were not included in this review, as they were outside of the five-year search period, but are listed in Appendix 5 as additional references of potential interest. Both studies concluded that UPA was cost-effective in preventing unwanted pregnancy.

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## Appendix 1: Selection of Included Studies



## Appendix 2: Characteristics of Included Studies

**Table 2: Characteristics of Included Economic Studies**

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Interventions	Cost included
Bellows et al., 2018 <sup>11</sup> United States Funding: internally	Cost-effectiveness 1 <sup>o</sup> outcome: ICER  Decision analytic model incorporated with Markov model of 1000 women seeking EC  Model inputs: from published literature and national sources  Treatment effects: Unintended pregnancy  Sensitivity analysis: 1-way, 2-way, probabilistic	Perspective: US payer perspective  Time horizon: 1-year  Currency: 2017 US dollars  No discount	Women of childbearing age and regular menstrual cycle presenting to a clinical setting for EC within 5 days of unprotected sexual intercourse  Age: 20 to 34 years	<ul style="list-style-type: none"> <li>- UPA</li> <li>- LNG</li> <li>- Cu IUD</li> <li>- LNG IUD</li> </ul>	Direct medical costs only <ul style="list-style-type: none"> <li>- Cost of pregnancy: \$5167</li> <li>- EC costs (\$43 for UPA, \$29 for LNG, \$887 for Cu IUD, \$917 for LNG IUD)</li> </ul>
Schmid, 2015 <sup>12</sup> France Funding: HRA Pharma	Cost-effectiveness 1 <sup>o</sup> outcome: ICER  Decision analytic model  Model inputs: from published literature and national sources  Treatment effects: Unintended pregnancy  Sensitivity analysis: 1-way, 2-way, probabilistic	Perspective: collective perspective  Time horizon: Period from unprotected intercourse until the moment termination occurred or, in the case of pregnancy carried to term, within 8 weeks after birth  Currency: 2015 euro  No discount	Young women in France presenting to a clinical setting for EC within 72 hours of unprotected sexual intercourse  Age: 15 to 17 years	<ul style="list-style-type: none"> <li>- UPA</li> <li>- LNG</li> </ul>	Direct costs of healthcare resources that are linked to the use of contraception and to termination or term delivery after unintended pregnancy  No indirect costs, transportation costs, or loss of productivity costs included

Cu = copper; EC = emergency contraception; ICER = incremental cost-effectiveness ratio; IUD = intrauterine device; LNG = levonorgestrel; UPA = ulipristal acetate

## Appendix 3: Quality Assessment of Included Studies

**Table 3: Quality Assessment of Economic Studies**

JBIChecklist for Economic Evaluations <sup>10</sup>	Bellows et al., 2018 <sup>11</sup>	Schmid, 2015 <sup>12</sup>
1. Is there a well-defined question?	Yes	Yes
2. Is there comprehensive description of alternatives?	Yes	Yes
3. Are all important and relevant costs and outcomes for each alternative identified?	Yes	Yes
4. Has clinical effectiveness been established?	Yes	Yes
5. Are costs and outcomes measured accurately?	Unclear	Unclear
6. Are costs and outcomes valued credibly?	Yes	Yes
7. Are costs and outcomes adjusted for differential timing? (Discount rate)	NA	NA
8. Is there an incremental analysis of costs and consequences?	Yes	Yes
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	Yes	Yes
10. Do study results include all issues of concern to users?	No	No
11. Are the results generalizable to the setting of interest in the review?	Unclear	Unclear

NA = not applicable

## Appendix 4: Main Study Findings and Author’s Conclusions

**Table 4: Summary of Findings of Economic Studies**

Main Study Findings	Author’s Conclusions
Bellows et al., 2018 <sup>11</sup>	
<p><b>Costs, pregnancies, and ICER of EC methods in 1000 women over 1 year</b></p> <ul style="list-style-type: none"> <li>– Mean cost: UPA (\$1,227,902); oral LNG (\$1,278,877)</li> <li>– Incremental cost (95% CI): LNG cost – UPA cost = \$50,975 (-\$22,788 to \$208,3920)</li> <li>– Mean pregnancies: UPA (137.2); oral LNG (150.0)</li> <li>– Incremental pregnancies prevented (95% CI): UPA pregnancies – LNG pregnancies = -12.8 (-29.7 to 1.1)</li> <li>– ICER (incremental cost per pregnancy prevented): -\$3,982 (Oral LNG was dominated by UPA, i.e., oral LNG cost more and prevented fewer pregnancies than UPA)</li> <li>– WTP threshold was set at \$5,167</li> </ul> <p><b>One-way sensitivity analysis</b></p> <ul style="list-style-type: none"> <li>– UPA was more cost-effective than oral LNG at all cases tested including proportion of obese women</li> </ul> <p><b>Probabilistic sensitivity analysis</b></p> <ul style="list-style-type: none"> <li>– UPA had higher probability of being most cost-effective compared to oral LNG at WTP ranging from \$0 to \$10,000.</li> </ul>	<p><i>“On average, oral levonorgestrel (LNG) cost more and was less effective than UPA”<sup>11</sup> p.e7</i></p>
Schmid, 2015 <sup>12</sup>	
<p><b>Incremental cost and effectiveness of UPA versus oral LNG</b></p> <p>Base case (intake within 72 hours)</p> <ul style="list-style-type: none"> <li>– Cost of unintended pregnancy per intake*: UPA (22.17 €); LNG (35.05 €)</li> <li>– Drug cost: UPA (23.57 €); LNG (7.41 €)</li> <li>– Cost per patient (cost of unintended pregnancy per intake + drug cost): UPA (45.76 €); LNG (42.46 €)</li> <li>– Incremental cost: UPA cost – LNG cost = 3.30 €</li> <li>– Pregnancy rate (%): UPA (1.36); oral LNG (2.15)</li> <li>– Incremental pregnancy rate prevented (%): LNG pregnancy rate – UPA pregnancy rate = 0.79</li> <li>– ICER (incremental cost per pregnancy prevented): 418.00 €</li> </ul> <p>Subgroup (intake within 24 hours)</p> <ul style="list-style-type: none"> <li>– Cost of unintended pregnancy per intake*: UPA (13.86 €); LNG (40.75 €)</li> <li>– Drug cost: UPA (23.57 €); LNG (7.41 €)</li> <li>– Cost per patient (cost of unintended pregnancy per intake + drug cost): UPA (37.45 €); LNG (48.16 €)</li> <li>– Incremental cost: UPA cost – LNG cost = -10.72 €</li> <li>– Pregnancy rate (%): UPA (0.85); oral LNG (2.50)</li> <li>– Incremental pregnancy rate prevented (%): LNG pregnancy rate – UPA pregnancy rate = 1.65</li> <li>– ICER (incremental cost per pregnancy prevented): -649.49 € (UPA dominant; more effective at lower cost)</li> </ul> <p><b>Univariate (one-way) sensitivity analysis</b></p> <p>Base case (intake within 72 hours)</p> <ul style="list-style-type: none"> <li>– UPA was dominant method at its lower cost (19.9 €)</li> </ul>	<p><i>“Ulipristal acetate dominates levonorgestrel when taken within 24 hours after unprotected intercourse, i.e., it is more effective at a lower cost. When taken within 72 hours, ulipristal acetate is a cost-effective alternative to levonorgestrel, given the cost of avoiding an additional pregnancy with ulipristal acetate is less than the average cost of these pregnancies. IN the light of these findings, it is worthwhile to provide free access to minors.”<sup>12</sup> p.1</i></p>

Main Study Findings	Author's Conclusions
<p>Subgroup (intake within 24 hours)</p> <ul style="list-style-type: none"> <li>- UPA was dominant method in five analyses (cost of UPA, cost of LNG, cost of birth, cost of miscarriage, and cost of termination)</li> <li>- UPA was dominant method at high value of pregnancy outcome</li> </ul> <p><b>Two-way sensitivity analysis (varied in rates of pregnancy in both drugs)</b></p> <ul style="list-style-type: none"> <li>- UPA remained dominant method in the majority of both base case and subgroup</li> </ul> <p><b>Probabilistic sensitivity analysis</b></p> <ul style="list-style-type: none"> <li>- At WTP of 1,630.10 €, UPA was the preferred method in 76.9% of cases, and it was superior (more cost effective at lower cost) to LNG in 45% of cases</li> </ul> <p>*Cost of unintended pregnancy per intake = cost of unintended pregnancy (1,630 €) multiplied with pregnancy rate of each drug</p>	

EC = emergency contraception; ICER = incremental cost-effectiveness ratio; LNG = levonorgestrel; UPA = ulipristal; WTP = willingness-to-pay

## Appendix 5: Additional References of Potential Interest

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