Common Drug Review

Pharmacoeconomic Review Report

December 2013

Drug	ulipristal acetate (Fibristal)
Indication	Treatment of moderate to severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery. The duration of treatment is limited to three months.
Listing request	As per indication
Manufacturer	Actavis Specialty Pharmaceuticals

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ABBREVIATIONS

AE	adverse event
CADTH	Canadian Agency for Drugs and Technology in Health
CDR	Common Drug Review
CI	confidence interval
DB	double blind
FDA	Food and Drug Administration
ICER	incremental cost-effectiveness ratio
LA	leuprolide acetate
MCS	Monte Carlo simulation
QALY	quality-adjusted life-year
SD	standard deviation
UA	ulipristal acetate
UF	uterine fibroids
WDAE	withdrawal due to adverse event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION[1]

Drug Product	Ulipristal acetate (Fibristal)
Study Question	In this evaluation, ulipristal acetate is compared with leuprolide acetate in order to determine its cost utility in pre-surgical patients with moderate to severe symptoms of uterine fibroids (UF).
Type of Economic Evaluation	Cost-utility analysis
Target Population	Women of reproductive age with moderate to severe symptoms of UFs who would be eligible for surgery
Treatment	Ulipristal acetate: 5 mg daily for a period of up to 90 days
Outcome	QALYs
Comparators	Leuprolide acetate: 3.75 mg intramuscular injection every four weeks for three doses
Perspective	Health care system (secondary analysis from the societal perspective)
Time Horizon	90 days
Manufacturer's Results (Base Case)	Ulipristal acetate is dominant compared with leuprolide acetate in that it is associated with more QALYs (gain of 0.012) and lower costs (cost savings of $85.10)
Key Limitations and CDR Estimate	• The major limitation with the analysis is the utility values employed — especially the utility values for uncontrolled bleeding and for oral administration. • In addition, analysis assumed differential utility values for patients with ulipristal acetate and leuprolide acetate for controlled bleeding. • Reanalysis was conducted using a lower disutility for uncontrolled bleeding, the same utility value for controlled bleeding, and no utility increment for oral administration. ○ Reanalysis still found ulipristal acetate to be dominant — QALY gains of 0.004 and cost savings of $85.33.

CDR = Common Drug Review; QALY = quality-adjusted life-year; UF = uterine fibroid.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION[1]

Background

The manufacturer compares ulipristal acetate (UA) with leuprolide acetate (LA) in women of reproductive age with moderate to severe symptoms of uterine fibroids (UFs) who would be eligible for surgery. UA is given as an oral medication at 5 mg per day for up to 90 days. The manufacturer submitted UA at a confidential price of $11.46 per 5 mg tablet for a three-month cost of $1,031. Alternatively, LA is delivered through a 3.75 mg intramuscular injection on a monthly basis for three months ($1,042 per three-month course).

Summary of Economic Analysis

The manufacturer conducted a cost-utility analysis with the base case from the health care system perspective. The target population is as per the Health Canada indication — women of reproductive age with moderate to severe symptoms of UFs who would be eligible for surgery. The analysis was conducted through the use of decision tree with four possible outcomes: controlled bleeding with and without hot flashes and uncontrolled bleeding with and without hot flashes. Efficacy data were derived from the PEARL II clinical trial. Three cost elements were included in the study: drug costs, other medical costs, and lost productivity. Utility values for each health state were obtained through a Web-based survey using health state descriptors and the EQ-5D instrument. The time horizon for the analysis was set at 90 days, which reflects the standard course of treatment.

Results of Manufacturer's Analysis

UA is found to be less expensive than LA ($1,279.92 compared with $1,365.02; a cost saving of $85.10) and more effective (0.177 compared with 0.165; quality-adjusted life-year [QALY] gains of 0.012) during a 90-day time horizon. Thus, UA dominates LA.

Interpretations and Key Limitations

The major limitations within the model related to the utility values adopted, particularly for uncontrolled bleeding, for oral administration and for bleeding control with UA and LA. The limitations overestimated the QALY gain from UA versus LA. However, reanalysis using more conservative assumptions led to the same conclusions as the manufacturer's base analysis.

Results of Common Drug Review Analysis

Reanalysis found UA to be dominant compared with LA: QALY gains of 0.004 and cost savings of $85.33 for UA.

Issues for Consideration

UA is the only licensed product for the treatment of women of reproductive age with moderate to severe symptoms of UF who would be eligible for surgery.

Conclusions

Both the manufacturer's base result and the Common Drug Review (CDR) reanalysis suggest that UA is more effective and less costly compared with LA.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION[1]

1. INTRODUCTION

1.1 Study Question

"In this evaluation, ulipristal acetate is compared with leuprolide acetate in order to determine its cost utility in pre-surgical patients with moderate to severe symptoms of UF."[1]

1.2 Treatment

As per submitted product — ulipristal acetate (UA) 5 mg daily for up to 90 days.

1.3 Comparator

Leuprolide acetate: 3.75 mg intramuscular injection every four weeks for three doses.

1.4 Type of Economic Evaluation

The analysis was conducted in the form of a cost-utility analysis — this is appropriate as per the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines, given that treatment is likely to improve the quality of life of patients, with no impact on mortality.

Primary analysis is from the health care system perspective, while a secondary analysis adopts a societal perspective. This is appropriate as per CADTH guidelines.

1.5 Population

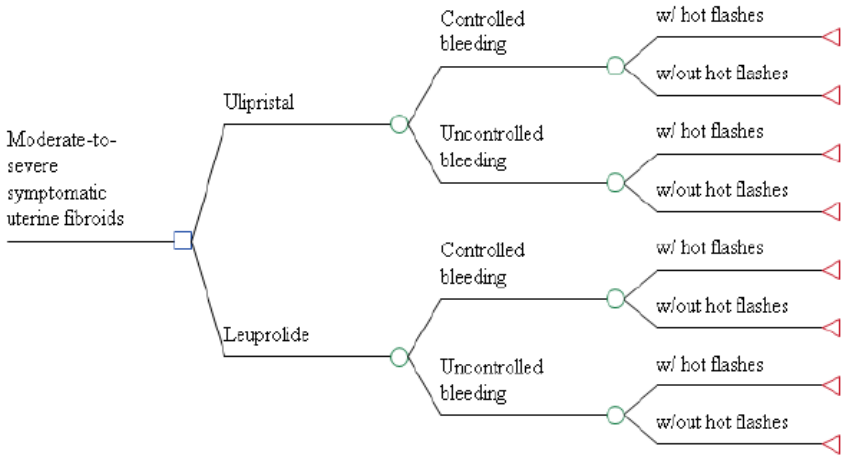
The target population is women of reproductive age with moderate to severe symptoms of UF who would be eligible for surgery. This is as per the Health Canada indication.

2. METHODS

2.1 Model Structure

Analysis is conducted through the use of decision tree with four possible outcomes: controlled bleeding with and without hot flashes, and uncontrolled bleeding with and without hot flashes (Figure 1).

FIGURE 1: MODEL DIAGRAM



Source: *Manufacturer's Pharmacoeconomic Submission*.[1]

2.2 Clinical Inputs

2.2.1 Efficacy

Efficacy data are derived from the PEARL II clinical trial.[2,3] Controlled bleeding was defined by a score on the Pictorial Blood Assessment Chart (PBAC) of < 75 (summed during the preceding 28-day period). The probabilities of controlled bleeding over three months were 0.891 for LA and 0.903 for UA. However, analysis also incorporated the time to bleeding control for patients who experienced controlled bleeding. This was obtained by conducting a Kaplan–Meier analysis of time to controlled bleeding. This analysis found that the duration of time with controlled bleeding was 84.8 days for UA and 79.8 days for LA, suggesting additional benefit not just in terms of the proportion of patients achieving control.

The analysis did not distinguish between the degrees of uncontrolled bleeding; i.e., this outcome was considered binary.

2.2.2 Harms

The major side effect of treatment was hot flashes, which was derived from the PEARL II clinical trial.[2,3] The probability of having hot flashes for UA was 11% (95% CI, 6.1 to 19.8) and for LA was 40% (95% CI, 30.2 to 49.8). Unlike with controlled bleeding, there were no temporal considerations with respect to hot flashes and they were assumed to be persistent and last the entire three-month period.

No other side effects were incorporated into the model.

2.2.3 Mortality

Given the short time horizon of the study, no consideration of mortality was given.

2.3 Costs

Three cost elements were included in the study:

- Drug costs
- Other medical costs
- Lost productivity.

2.3.1 Drug Costs

Drug costs were based on the acquisition cost of leuprolide acetate and ulipristal acetate and incorporated both a pharmacist's markup and a dispensing fee. One additional dispensing fee was assumed with UA.

2.3.2 Administration Costs

The costs of injection visits for LA were included based on physician fees for a regular visit, plus fees for administration of an injection.

Other Medical Costs

It was assumed that there would be one additional obstetrician–gynecologist (OB/GYN) surgery consult with LA and UA, and a further OB/GYN follow-up visit with UA.

Societal Costs

For the secondary analysis from a societal perspective, the costs of absenteeism were incorporated. This was based on hourly wage rates for females and assuming two hours of lost productivity per visit.

Costs of Adverse Effects

In sensitivity analysis, an additional cost was assigned to LA in the form of add-back therapy, which was a month's treatment with norethindrone acetate.

2.4 Utilities

Utility values were obtained for the following: controlled bleeding, uncontrolled bleeding, utility incremental for oral administration and utility decrement for hot flashes. These were obtained by the following process (Hux et al. 2013):[4]

- Draft health state descriptions were obtained through a literature review.
- These draft health states were validated through clinician review.
- A pilot study of valuation for each state was conducted by four women.
- A Web-based survey was conducted. Women with no previous history of UF were presented with the states and completed the EQ-5D, assuming they were in these states.
- Based on the survey responses, utility value for each health state was obtained.

Four distinct utility values were estimated, which were converted into daily utility weights (i.e., divided by 365): controlled bleeding (0.73), uncontrolled bleeding (0.55), utility incremental for oral administration (0.02), and utility decrement for hot flashes (0.06).

Based on the utility values obtained, outcomes in terms of QALYs for UA were thus a function of the following:

- daily utility values for uncontrolled bleeding and for controlled bleeding
- probability of patients achieving controlled bleeding with UA, and for those achieving control, the number of days with bleeding control
- the probability of hot flashes with UA and the disutility value for hot flashes
- utility increment for oral administration.

For LA, the above applies, except there was no utility increment for oral administration, given that it involves an intramuscular injection.

2.5 Time Horizon

Time horizon is 90 days with no cycle length, given that the study took the form of a decision tree analysis. This is appropriate as per CADTH guidelines.

2.6 Discounting

No discounting was conducted, given the short time horizon. This is appropriate as per CADTH guidelines.

2.7 Validation

No formal validation was conducted. All clinical data are derived from the PEARL II trial,[2,3] which suggest these are valid. Utility data are derived from a survey, the validity of which is questioned; see below.

3. RESULTS

3.1 Manufacturer's Base Case[1]

Base results are obtained from a Monte Carlo simulation (MCS) with 1,000 replications. Results are very consistent with the deterministic results.

UA is found to be less expensive (cost saving of $85.10) and more effective (QALY gains of 0.012).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

Drug	Total Costs ($)	Incremental Cost of UA ($)	Total QALYs	Incremental QALYs of Ulipristal	Incremental Cost per QALY
LA	1,365.02		0.165		
UA	1,279.92	–85.10	0.177	0.012	dominant

LA = leuprolide acetate; QALY = quality-adjusted life-year; UA = ulipristal acetate.
Source: *Manufacturer's Pharmacoeconomic Submission*.[1]

3.2 Summary of Manufacturer's Sensitivity Analyses

3.2.1 One-way Sensitivity Analyses

- A sensitivity analysis was conducted, removing the utility increment for oral administration and utility decrement for hot flashes. UA remained dominant over LA.
- Analysis from the societal perspective found UA to be dominant over LA.
- Analysis assuming no medical visit costs for LA injections found UA to be more expensive (incremental cost of $16.98) with an incremental cost per QALY gained of $1,493.
- Analysis assuming 11.25 mg of LA given at one visit found UA to be more expensive (incremental cost of $8.87) with an incremental cost per QALY gained of $748.

3.2.2 Probabilistic Sensitivity Analysis

- Base results were based on an MCS with 1,000 replications. UA was more effective in terms of QALYs (range 0.04 to 0.196) and cost saving (range $11 to $177) — i.e., dominant — in all replications.
- Analysis adopted correct functional forms for all probability distributions and the MCS was conducted appropriately.

3.3 CDR Analyses

Reanalysis was conducted, adopting the following alternative assumptions (explanation provided in Section 4 below):

- Utility decrement from uncontrolled bleeding of 0.09 rather than 0.18.
- No utility increment for oral medication.
- For patients achieving bleeding control, the time to bleeding control was assumed to be the same for both treatments.

TABLE 3: CDR REANALYSIS

Drug	Total Costs ($)	Incremental Cost of UA ($)	Total QALYs	Incremental QALYs of Ulipristal	Incremental Cost per QALY
LA	1,365.20		0.170		
UA	1,279.86	–85.34	0.174	0.004	dominant

LA = leuprolide acetate; QALY = quality-adjusted life-year; UA = ulipristal acetate.

Given that UA dominates LA in both the manufacturer-submitted analysis and the CDR reanalysis, all analyses relating to price reduction (10% to 90% price reduction for UA) resulted in UA remaining dominant over LA.

4. DISCUSSION

The major limitation with the submitted analysis relates to the utility elicitation exercise. The utility values obtained for controlled and uncontrolled bleeding lack a degree of face validity — the utility difference of 0.18 appears excessive. This can be explained by reviewing the scenario descriptions for both controlled bleeding and uncontrolled bleeding (Table 4).

TABLE 4: HEALTH STATE DESCRIPTORS

Uncontrolled Bleeding	Controlled Bleeding
You have been told by your doctor that you have one or more fibroids or non-cancerous lumps of tissue in your uterus. You are being given a medicine injected in your arm or buttocks once a month for this.	You have been told by your doctor that you have one or more fibroids or non-cancerous lumps of tissue in your uterus. You are being given a medicine injected in your arm or buttocks once a month for this.
Your abdomen may look somewhat enlarged and you may feel abdominal pressure. You may sometimes need to urinate frequently or have urinary urges and you may be constipated.	Your abdomen may look somewhat enlarged and you may feel abdominal pressure. You may sometimes need to urinate frequently or have urinary urges and you may be constipated.
Your menstrual periods last for more than two weeks each month, with very heavy menstrual bleeding or flooding. You wear pads and tampons together and need to change them often and worry about bleeding showing through clothing in public, which can be embarrassing.	Your menstrual periods are shorter than usual and there is a lighter amount of bleeding because of the medication. You may not have any menstrual bleeding.
You need to stay near a bathroom and may be homebound because of this.	You feel tired much of the day, which affects your ability to work, to take care of your home or family, and to socialize or take part in hobbies.
You feel tired much of the day, which also affects your ability to work, to take care of your home or family, and to socialize or take part in hobbies.	You sometimes feel moody, irritable, or depressed.
You have substantial abdominal pain and cramping during your periods. Abdominal pain can spread to your back, tailbone, and down your legs, and pain can continue between periods.	Menstrual problems prevent you from enjoying your sex life.
You often feel moody, irritable, and depressed.	
You feel embarrassed talking to a doctor or to family members about your symptoms.	
Menstrual problems prevent you from enjoying your sex life.	

Source: *Manufacturer's Pharmacoeconomic Submission*.[1]

Bleeding control is treated as a dichotomy in the model — i.e., a patient will transition directly from uncontrolled bleeding to controlled bleeding. The descriptions provided here appear to suggest this is unlikely. The description of uncontrolled bleeding appears to be extremely negative. Given this, the utility difference of 0.18 is probably a biased estimate and CDR reanalysis adopted a utility difference of half this amount (i.e., utility values of 0.73 and 0.64).

The utility increment of 0.02 for oral medication appears high, given that injections are at most once a month. The results for this state appear unlikely: the survey suggests that daily oral medication improves mobility, with 55.9% of women reporting "no problems in walking about" compared with 47.4% with monthly injections. Given these concerns, reanalysis assumed no utility increment with oral medication.

Finally, although analysis took the form of a simple decision tree, different utility values were assumed for UA and LA for patients achieving bleeding control due to modelled differences in time to bleeding control. To preserve the decision tree format of the model, reanalysis assumed the average utility value for control for both treatments.

These limitations do not substantially affect the manufacturer's results, in that UA remains dominant over LA. Thus, none of these limitations can be considered "key."

4.1 Issues for Consideration

- There were no further studies conducted by any health technology assessment bodies relating to the use of UA in the treatment of UF. However, there was one Hungarian study conducted by Nagy et al.,[5] which is available in abstract only.
- A further issue for consideration is the lack of available treatments licensed for this condition.

4.2 Patient Input

Based on the CDR Patient Input process, patient groups indicated that:

- … tumours cause mental, physical, emotional, financial, and sexual side effects, including pain, pressure, extreme blood loss during menstruation, the need for emergency blood transfusions, debilitating exhaustion, anemia, cognitive impairment such as memory loss and confusion, lost wages, greater-than-average expenses for menstrual supplies, adult diapers, medications, and cleaning expenses, and quality of life costs such as missed family life and social engagements.
- In addition, implications for infertility were stated to be issues for patients.

While the manufacturer did consider a broader perspective (societal) in its submission, other outcomes of interest were not considered by the manufacturer explicitly, but rather through the utilities associated with the health states.

5. CONCLUSIONS

The manufacturer's base result suggests that UA is cost-effective compared with LA in that it is both more effective and less costly. The CDR review identified certain weaknesses with assumptions made, and revised values for certain parameters were adopted in reanalysis. However, analysis reached the same conclusion as the manufacturer's submission in that UA was dominant over LA.

APPENDIX 1: COST COMPARISION TABLE

The comparators presented in the table below have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 5: COST COMPARISON TABLE FOR FIBRISTAL

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average 90-Day Drug Cost ($)
UA (Fibristal)	**5 mg**	**Tab**	**11.4600***	**5 mg daily for 3 months**	**11.46**	**1,031**
Treatments not specifically indicated but used for the management of symptoms of UF						
Buserelin acetate (Suprefact)	1 mg/mL	10 mL nasal spray	79.3700	200 mcg in each nostril 3 times daily for up to 6 to 9 months	9.52	857
Goserelin acetate (Zoladex)	3.6 mg	inj	390.5000	Once every 28 days	13.95	1,255
	10.8 mg		1113.0000	Once every 13 weeks	12.23	1,101
LA (Lupron depot)	3.75 mg	inj	347.1800	Once monthly for up to 6 months	11.57	1,042
	11.25 mg		1034.4100	Once every 3 months for up to 6 months	11.49	1,034
Nafarelin acetate (Synarel)	2 mg/mL	8 mL nasal spray	285.9000[b]	200 mcg twice daily for up to 6 months	7.15	643
Triptorelin pamoate (Trelstar)	3.75 mg	inj	327.1100	Once every 28 days for up to 6 months	11.68	1,051

inj = injection; LA = leuprolide acetate; tab = tablet; UA = ulipristal acetate; UF = uterine fibroid.
[a]Manufacturer's confidential submission price.[1]
[b]Saskatchewan Formulary (June 2013).[7]
Source: Ontario Drug Benefit Formulary (June 2013),[6] unless otherwise indicated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

When considering only costs, outcomes and quality of life, how attractive is UA relative to LA?

UA Versus LA	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Dominant					

CE = cost-effectiveness; LA = leuprolide acetate; NA = not applicable; UA = ulipristal acetate.

The above is based on both the manufacturer's results and the reanalysis.

APPENDIX 3: ADDITIONAL INFORMATION

SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

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	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

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