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Reimbursement Recommendation

Leuprolide Mesylate (Camcevi)

Indication: For the treatment of adult patients with advanced prostate cancer
Sponsor: Accord Healthcare Inc.
Final Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Camcevi?

Canada's Drug Agency (CDA-AMC) recommends that Camcevi should be reimbursed by public drug plans for the treatment of adult patients with advanced prostate cancer if certain conditions are met.

Which Patients Are Eligible for Coverage?

Camcevi should only be covered to treat adult patients with prostate cancer according to the reimbursement criteria used by public drug plans for androgen deprivation therapies (ADTs) for the treatment of prostate cancer.

What Are the Conditions for Reimbursement?

The cost of Camcevi should not exceed the drug program cost of treatment with the least costly alternative treatment.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that treatment with Camcevi effectively suppressed and maintained low serum testosterone levels over time in adult patients with prostate cancer.
- Camcevi provides an additional formulation option of ADT that is effective and offers a long dosing interval.
- Based on the CDA-AMC assessment of the health economic evidence, Camcevi may represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Camcevi compared with other ADTs; therefore, the cost of Camcevi should not exceed the drug program cost of treatment with the least costly ADT reimbursed for the treatment of prostate cancer.
- Based on public list prices, Camcevi is estimated to save public drug plans approximately $700,000 over the next 3 years.

Additional Information

What Is Advanced Prostate Cancer?

Advanced prostate cancer refers to prostate cancer that has a severe diagnosis and prognosis, requiring treatment that lowers testosterone levels. It is estimated that 27,900 patients in Canada were diagnosed in 2024.

Summary

Unmet Needs in Advanced Prostate Cancer

Patients have previously identified a need for ADTs that can effectively suppress testosterone levels, delay disease progression, prolong life, have fewer side effects, improve quality of life (QoL), and can be administered or accessed with ease.

How Much Does Camcevi Cost?

Treatment with Camcevi is expected to cost approximately $2,998 per patient annually.

Recommendation

The CDA-AMC pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that leuprolide mesylate be reimbursed for the treatment of adult patients with advanced prostate cancer only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from a phase III, single-arm, open-label trial (FP01C-13-001) (N = 137) demonstrated that treatment with leuprolide mesylate, a 6-month depot injection, may result in a clinical benefit for adult patients with histologically confirmed prostate carcinoma. Leuprolide mesylate suppressed serum testosterone to the castrate level (≤ 50 ng/dL) in 98.5% (95% confidence interval [CI], 94.8% to 99.8%) of the intention-to-treat (ITT) population by day 28 following the first dose of leuprolide mesylate and maintained the castrate testosterone level in 97.0% (95% CI, 92.2% to 98.9%) of the ITT population by day 336. There was a low incidence of testosterone excursions higher than 50 ng/dL during the follow-up period.

Due to the single-arm design of the FP01C-13-001 trial and the lack of the indirect comparative evidence, pERC was unable to draw a conclusion on the relative efficacy between leuprolide mesylate and other ADTs currently available in Canada. Nonetheless, pERC acknowledged that the single-arm study design and the selection of efficacy end points in the FP01C-13-001 trial met the regulatory requirements to establish the efficacy and safety of gonadotropin hormone-releasing hormone (GnRH) analogues for advanced prostate cancer. pERC also recognized that leuprolide mesylate is a new salt formulation of leuprolide that has been used broadly for the treatment of prostate cancer for several decades.

Patients have previously identified a need for ADTs that can effectively suppress testosterone levels, delay disease progression, prolong life, have an acceptable safety profile, improve QoL, and can be administered or accessed with ease. Based on the evidence reviewed, pERC concluded that leuprolide mesylate met some of these needs as it effectively suppresses and/or maintains serum testosterone at castrate levels and provides an additional formulation option for patients which offers a long dosing interval.

At the sponsor-submitted price for leuprolide mesylate and publicly listed prices for other ADTs, leuprolide mesylate was less costly than other ADTs. Due to a lack of indirect evidence comparing leuprolide mesylate to other ADTs, there is insufficient evidence to support a price premium for leuprolide mesylate over other ADTs. Therefore, the total drug cost of leuprolide mesylate should not exceed the total drug cost of other ADTs.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, discontinuation, and prescribing		
1. Reimbursement of leuprolide mesylate should be based on the criteria used by each of the drug plans for initiation, renewal, discontinuation, and prescribing of ADTs for the treatment of prostate cancer.	Evidence from the single-arm FP01C-13-001 trial demonstrated that treatment with leuprolide mesylate may result in a clinical benefit for patients (aged 18 years and older) with prostate carcinoma. There is insufficient evidence to suggest that leuprolide mesylate should be held to a different standard than other ADTs currently reimbursed in Canada for the treatment of prostate cancer.	—
Pricing		
1. Leuprolide mesylate should be negotiated so that it does not exceed the drug program cost of treatment with the least costly ADT reimbursed for the treatment of prostate cancer.	As no direct or indirect evidence was submitted comparing leuprolide mesylate with other ADTs, there is insufficient evidence to justify a cost premium for leuprolide mesylate over the least expensive ADT reimbursed for prostate cancer.	—

ADT = androgen deprivation therapy.

Discussion Points

- **Unmet needs**: pERC discussed that leuprolide products have been used for the treatment of prostate cancer in clinical practice for over 3 decades. Leuprolide mesylate is a new salt formulation of leuprolide that has a 6-month dosing interval and does not require reconstitution during preparation. While pERC agreed with the clinical experts that the addition of leuprolide mesylate may not address one of the major unmet needs for currently available leuprolide products (i.e., prevent development of refractory disease or castrate resistance after long-term use), pERC concluded that leuprolide mesylate provides an additional 6-month depot formulation option which may be considered convenient for some patients, and may improve accessibility and ease of drug preparation for health care providers.
- **Certainty of evidence**: pERC discussed the evidence submitted by the sponsor and was unable to draw a conclusion on the relative efficacy of leuprolide mesylate to any of the ADTs currently available in Canada given the absence of direct and indirect comparative evidence. Additionally, survival end points (e.g., overall survival [OS] or progression-free survival) were not evaluated in the FP01C-13-001 trial. Yet, pERC acknowledged that the single-arm design and selection of efficacy end points in the FP01C-13-001 trial aligned with current regulatory guidance in establishing the efficacy of leuprolide products and were also considered appropriate and adequate by the clinical experts consulted by CDA-AMC. pERC also considered clinical expert input that the efficacy of

leuprolide mesylate was comparable to the other leuprolide products currently used in Canada. pERC noted that leuprolide mesylate would serve as an additional effective ADT option for prostate cancer.

- **Harms**: pERC discussed the harms results on leuprolide mesylate (2 years of total exposure) from the pivotal FP01C-13-001 trial and the safety extension single-arm study, FP01C-13-001-EX. pERC noted that conclusions on the comparative safety of leuprolide mesylate could not be drawn from the sponsor-submitted evidence due to the absence of direct and indirect comparative evidence. Based on clinical expert input, the safety profile of leuprolide mesylate was consistent with those reported for the currently available leuprolide products. pERC noted that leuprolide mesylate appeared to be safe and tolerable for the duration of the studies, although its long-term safety remains uncertain and further research is warranted given that this drug is typically given to patients for life.
- **Quality of life**: Patients identified a need for treatments that improve QoL. pERC was unable to conclude the impact of leuprolide mesylate on QoL due to a potential risk of performance and detection bias associated with the single-arm, open-label study design of the FP01C-13-001 trial.
- **Generalizability**: pERC noted that the Health Canada–approved indication targets patients with advanced prostate cancer, while the FP01C-13-001 trial did not limit the enrolment to patients with advanced prostate cancer but included patients with stage I to stage IV prostate carcinoma. pERC acknowledged that there is no universal definition for advanced prostate cancer. Clinical exert input indicated that advanced prostate cancer commonly refers to biochemically recurrent and metastatic disease, yet patients with intermediate or high-risk localized prostate cancer can also be eligible for treatment with leuprolide products. pERC considered input from the clinical experts and agreed that the results from the FP01C-13-001 study population were likely overall generalizable to the patient population expected to receive leuprolide mesylate in Canada.
- **Current status of ADTs in Canada**: Currently, each of the public drug plans in Canada have established their own reimbursement criteria for existing ADTs for the treatment of prostate cancer. pERC acknowledged that it would be most appropriate with the least interruption of current reimbursement status by aligning the reimbursement criteria of leuprolide mesylate with the criteria for the existing ADTs of each public drug plan.

Background

Prostate cancer is one of the most commonly diagnosed cancers in males in Canada, with an estimated 27,900 patients diagnosed in 2024 and accounting for 22% of all new cancer cases in males. Prostate cancer is also one of the most common causes of cancer deaths in Canada, with an estimate of 5,000 deaths in 2024. The median age of diagnosis is 66 years, with 20% aged 75 years and older. Most patients with prostate cancer do not have initial or early symptoms. As a tumour grows locally or once it metastasizes, symptoms can intensify and start to interfere with the physiological functions of the body. Diagnostic tests for prostate cancer include blood screening for prostate-specific antigen (PSA), physical digital rectal examination, biopsy of the prostate, and imaging through CT or MRI scans. The tumour-node-metastasis classification system is commonly used to determine the tumour stage of prostate cancer, which involves 4

stages (stage I to stage IV); the higher the stage, the more the tumour has spread. Terms, such as localized prostate cancer (limited to only in the prostate), locally advanced prostate cancer (spread outside of the prostate but not metastatic), and metastatic prostate cancer (spread beyond the tissues surrounding the prostate to lymph nodes or other parts of the body such as the lungs, liver, or bones), are used to describe the growth and spread of prostate cancer. Patients with localized prostate cancer at the time of diagnosis are reported to have a nearly 5-year OS rate of 100%, where patients with distant metastases only have a 5-year OS rate of 29%.

Both the sponsor and the clinical experts consulted by the CDA-AMC review team noted that ADT is a key component of systemic anticancer treatment of metastatic prostate cancer. According to the clinical experts consulted by the review team, ADT is given continuously throughout a patient's life after diagnosis and other medicines are used on top of ADT; ADT is typically continued when a patient's disease progresses or when a patient transitions to best supportive care near the end of life. The clinical experts also noted that some treatment protocols use ADT for a finite period (e.g., as "neoadjuvant" treatment before definitive surgery or radiotherapy), or as adjuvant therapy with radiotherapy. GnRH analogues, a type of ADT, are available as antagonists such as degaralix and relugolix or GnRH agonists such as leuprolide products including Eligard, Lupron Depot, Zoladex, and Zeulide Depot. The main goals in the treatment of advanced prostate cancer are to delay disease progression by achieving castrate levels of testosterone, which is defined as less than 50 ng/dL by the American Urological Association and European Association of Urology. The European Association of Urology further indicated that testosterone levels of less than 20 ng/dL might be associated with an improvement in outcomes, compared to the levels in the range between 20 and 50 ng/dL.

This is a tailored review submission of a new salt formulation of leuprolide, leuprolide mesylate (Camcevi). Leuprolide mesylate has been approved by Health Canada for the treatment of adult patients with advanced prostate cancer. Leuprolide mesylate is a GnRH analogue. It is a premixed product and available as an extended-release emulsion for injection. The dosage recommended in the product monograph is 42 mg administered every 6 months as a single subcutaneous injection.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, multicentre, single-arm, open-label pivotal study (FP01C-13-001) in adult patients with histologically confirmed prostate carcinoma with a baseline morning serum testosterone level greater than 150 ng/dL; and 1 phase III, single-arm, open-label, safety extension study (FP01C-13-001-EX)
- no patient input was received for the current review (input from a previous reimbursement review of an ADT for the same Health Canada indication [relugolix] was referenced)
- input from public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with prostate cancer

- input from 1 clinician group, Ontario Health Cancer Care Ontario Genitourinary Cancers Drug Advisory Committee (OH [CCO] GU DAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Group Input

No patient group input was received by the CDA-AMC review team for this review. Patient group input was summarized from a previous reimbursement review of relugolix (project number PC0342; final recommendation issued on July 22, 2024). Leuprolide mesylate and relugolix are both ADTs and share the same Health Canada indication. Despite relugolix being a GnRH antagonist and leuprolide mesylate a GnRH agonist, patient input collected from relugolix may serve as a reasonable proxy in aspects such as disease experience and unmet treatment needs. The patient group input from relugolix identified challenges in managing side effects associated with ADTs such as fatigue, weight gain, muscle loss, osteoporosis, hot flashes, cardiovascular risk, depression, and sexual dysfunction, and how such side effects can lead to depression and insomnia. The patient group input also identified the treatment needs, including prolonging life, delaying the progression of cancer, improving QoL, decreasing PSA levels, and minimizing side effects.

Clinician Input

Input From Clinical Experts Consulted for This Review

According to the clinical experts consulted by the CDA-AMC review team, there is no universal definition for advanced prostate cancer, and “patients with advanced prostate cancer” noted in the Health Canada–approved indication is subject to interpretation. The clinical experts consulted by the CDA-AMC review team noted that ADT can be used in intermediate and high-risk localized prostate cancer as well as in the context of biochemically recurrent and metastatic disease which would be the more common definition of advanced prostate cancer. According to the clinical experts consulted by the CDA-AMC review team, for patients with biochemically recurrent or metastatic disease, the treatment goal is to achieve castrate testosterone levels thereby controlling the disease by decreasing PSA, delaying development of metastatic disease (in the context of biochemical recurrence), reducing disease burden (in metastatic prostate cancer), which often results in improved symptoms, OS, and progression-free survival. According to the clinical experts consulted by the review team, long-term use of ADT with currently available GnRH analogues typically results in the development of refractory disease or castrate resistance, which was considered one of the main unmet needs. Leuprolide mesylate, as a GnRH analogue, does not address this major unmet need in the clinical experts’ opinion. According to the clinical experts consulted by the CDA-AMC review team, the availability of leuprolide mesylate, which does not require reconstitution like Eligard does, provides an additional formulation option for patients and clinicians.

According to the clinical experts consulted by the review team, there are currently several approved preparations of leuprolide products in Canada including Lupron Depot (3-month, 4-month, and 6-month

depots given as intramuscular injections), Eligard (1-month, 3-month, 4-month, and 6-month depots given as subcutaneous injections), and Zoladex (3-month depot given as subcutaneous pellet implants), and despite the prescribing heterogeneity across Canada, most patients are not on the 6-month preparations. The clinical experts consulted by the review team noted that leuprolide mesylate is not expected to shift the current treatment paradigm; rather, leuprolide mesylate would share the same place in therapy as other GnRH analogues and provide an additional option to the existing GnRH analogues.

According to the clinical experts consulted by the review team, patients with advanced prostate cancer are most likely to respond to treatment with leuprolide mesylate. The clinical experts consulted by the review team noted that the indications for GnRH analogue injections for patients with advanced prostate cancer have been well-established for several decades, and there are several other drugs with similar chemical formulation and pharmaceutical action already on the market. According to the clinical experts consulted by the review team, there are no particular disease characteristics which would warrant or contraindicate the use of leuprolide mesylate relative to other GnRH analogues, and there are no identifiable patient or disease features (clinical, histological, or biochemical), which render the patients more suited to leuprolide mesylate compared with other GnRH analogues.

According to the clinical experts consulted by the review team, the outcomes measured for advanced prostate cancer treatment used in clinical practice are aligned with those used in clinical trials. The clinical experts consulted by the review team noted that in advanced prostate cancer, efficacy was determined via evaluating a number of metrics including clinical status of the patient, radiologic response or progression, and PSA dynamics. The clinical experts consulted by the review team noted that current clinical guidelines are well-established for “clinically meaningful” response and should not vary among physicians, and the parameters applied to leuprolide mesylate should be identical to those already accepted for other GnRH analogue agents. The clinical experts consulted by the CDA-AMC review team noted that serum testosterone levels of 50 ng/dL or less is an accepted surrogate end point for efficacy and that recent evidence suggests that suppression of serum testosterone levels to less than 20 ng/dL might be associated with better biochemical relapse free survival.

According to the clinical experts consulted by the review team, ADT with GnRH analogues are typically intended to be given lifelong; however, in some instances, GnRH analogues are prescribed for a finite period as an adjunct to other definitive therapies (e.g., as neoadjuvant treatment before surgery, or neoadjuvant and adjuvant therapy to radiotherapy). The clinical experts consulted by the review team noted that GnRH analogue therapy is typically not discontinued even when there is disease progression or when a patient transitions to best supportive care near the end of life; instead, other medicines are added to ADT. According to the clinical experts consulted by the review team, occasionally, ADT with GnRH analogues may be discontinued due to significant or intolerable side effects at the patients’ or clinicians’ discretion.

According to the clinical experts consulted by the review team, appropriate treatment settings for leuprolide mesylate include outpatient or ambulatory care clinics, physicians’ offices, and injection clinics in the community setting. The clinical experts consulted by the review team also noted that treatment may also be given via a home injection program by nursing personnel. According to the clinical experts consulted by the

review team, a specialist (most commonly a urologist) usually establishes the diagnosis; treatment may be rendered by a urologist, a radiation oncologist, or a medical oncologist depending on the stage of disease; and monitoring is provided by either specialists or by primary care physicians depending on treatment response and stability of disease.

Clinician Group Input

The clinician group input on the review of leuprolide mesylate was received from 1 clinician group, OH (CCO) GU DAC. A total of 2 clinicians provided the input.

According to the OH (CCO) GU DAC, the treatment goals for patients with hormone-dependent advanced prostate cancer are to improve survival, delay disease progression, reduce cancer-related complications (e.g., skeletal related events with reduced need for palliative radiotherapy, spinal cord compression, urinary obstruction, need for palliative procedures such as transurethral resection of the prostate), improve patients' QoL, maintain independence of patients, and reduce the burden on caregivers. The OH (CCO) GU DAC noted that there are unmet needs for effective methods of suppressing testosterone with reduced side effects among patients with advanced prostate cancer as well as for reducing the drug costs among these patients.

According to the OH (CCO) GU DAC, leuprolide mesylate is a 6-month depot injection, and Eligard 6-month depot injection is currently available and reimbursed in Canada. According to the OH (CCO) GU DAC, leuprolide mesylate may improve convenience for some patients who prefer a 6-month dosing schedule due to their lifestyle, location of residence, as well as their ability to travel to get treatment, to have vacations, or to work. According to the OH (CCO) GU DAC, leuprolide mesylate would not change the current treatment paradigm but would provide an alternative to the 6-month Eligard product. According to the OH (CCO) GU DAC, any patients who require GnRH agonist therapy for prostate cancer would be candidates for leuprolide mesylate. The OH (CCO) GU DAC noted that the selection of leuprolide mesylate versus other available agents would be based mostly on the preferences of the prescriber and patients for a longer, 6-month injection interval.

According to the OH (CCO) GU DAC, testosterone levels, PSA response, and radiographic response are used to determine whether a patient is responding to treatment in clinical practice and in clinical trials. The OH (CCO) GU DAC noted that a common standard follow-up would be a PSA level with testosterone every 3 months and interval imaging depending on the scenario. The OH (CCO) GU DAC also noted that for patients with symptoms related to either locally advanced disease or metastatic disease, a clinically meaningful response is reduction or resolution of urinary tract obstruction or pain from bone metastases. The magnitude of response is standard across prescribers and should not depend on the agent chosen if the testosterone level is suppressed adequately.

Similar to the clinical experts consulted by the review team, the OH (CCO) GU DAC noted that for patients with metastatic prostate cancer, current available evidence supports the continuation of GnRH agonist therapy indefinitely through the next lines of therapy, even with disease progression. The OH (CCO) GU DAC noted that GnRH agonist therapy will be discontinued for severe intolerance or side effects that significantly interfere with patients' QoL. The OH (CCO) GU DAC noted that community, academic, outpatient, and hospital settings are all appropriate for treatment with leuprolide mesylate.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs (Table 2).

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
There was no comparator used in the FP01C-13-001 and FR01C-13 to 001-EX (single-arm trial) trials. Relevant comparators include leuprolide, goserelin, buserelin, degarelix, and relugolix.	This is a comment from the drug plans to inform pERC deliberations.
Considerations for continuation or renewal of therapy	
The primary efficacy end points were the percentage of patients with a serum testosterone ≤ 50 ng/dL by day 28 and the percentage of patients with testosterone ≤ 50 ng/dL from day 28 through day 336. Is this appropriate for monitoring therapeutic response?	According to the clinical experts consulted by the review team, in clinical practice, serum testosterone levels are monitored as biochemical response (not as clinical response) to ensure patients have achieved castrate testosterone levels after receiving ADT. The clinical experts consulted by the review team noted that defining castrate testosterone levels as suppression of serum testosterone levels ≤ 50 ng/dL was appropriate. The clinical experts consulted by the review team also noted that recent evidence suggests that suppression of serum testosterone levels to less than 20 ng/dL might be associated with better biochemical relapse free survival. The clinical experts consulted by the review team noted that monitoring the serum testosterone levels at day 28 was appropriate. Given leuprolide mesylate is a 6-month preparation, the clinical experts consulted by the review team noted that monitoring the serum testosterone levels close to 6 months after injection would be very informative to determine whether leuprolide mesylate could maintain the castrate testosterone levels. pERC acknowledged input from the clinical experts and noted that the renewal criteria of leuprolide mesylate should align with the criteria used by each of the drug plans for renewal of ADTs for the treatment of prostate cancer.
Considerations for discontinuation of therapy	
In the extension study (FR01C-13 to 001-EX), 30 patients went on to receive an additional 2 doses, for a total treatment duration of 2 years. There is no safety or efficacy data beyond 2 years. **Question**: What are the discontinuation criteria?	According to the clinical experts consulted by the review team, ADT is intended to be given lifelong. The clinical experts consulted by the review team noted that ADT is typically not discontinued even when there is disease progression or when a patient who transitions to best supportive care nears the end of life; instead, other medicines are added to ADT. According to the clinical experts consulted by the review team, occasionally, ADT may be discontinued due to significant or intolerable side effects at the patients' or clinicians' discretion. pERC acknowledged input from the clinical experts and noted

Drug program implementation questions	Response
	that the discontinuation criteria of leuprolide mesylate should align with the criteria used by each of the drug plans for discontinuation of ADTs for the treatment of prostate cancer.
Considerations for prescribing of therapy	
No concomitant anticancer therapies were permitted in the trial. Concomitant radiation was not permitted. Can leuprolide mesylate be used in combination with other treatments for prostate cancer?	pERC agreed with the clinical experts consulted by the review team that while it is acceptable in the clinical trial setting to not allow concomitant anticancer therapies, in clinical practice leuprolide mesylate could be used in combination with other prostate cancer treatments.
Generalizability	
Patients with an ECOG PS > 2 were excluded from the trial. Can patients with an ECOG PS > 2 be considered eligible?	The clinical experts consulted by the review team noted that patients with an ECOG PS > 2 may be considered eligible for leuprolide mesylate. pERC acknowledged input from the clinical experts and noted that the reimbursement criterion on ECOG PS of leuprolide mesylate should align with the criteria used by each of the drug plans for renewal of ADTs for the treatment of prostate cancer.
Funding algorithm	
Request an initiation of a rapid provisional funding algorithm	This is a comment from the drug plans to inform pERC deliberations.
Drug may change place in therapy of comparator drugs	This is a comment from the drug plans to inform pERC deliberations.
Consider aligning the reimbursement criteria of leuprolide mesylate with criteria for other leuprolide treatments currently available in Canada.	This is a comment from the drug plans to inform pERC deliberations.
In what situations would leuprolide mesylate be preferred over other ADT options?	Neither clinical expert consulted by the review team identified a situation in which selection of leuprolide mesylate over other ADT options is absolutely necessary. According to the clinical experts consulted by the review team, there are no particular disease characteristics which would warrant or contraindicate the use of leuprolide mesylate relative to other GnRH analogues, and there are no identifiable patient or disease features (e.g., clinical, histological, or biochemical), which render the patients more suited for leuprolide mesylate over other GnRH analogues. pERC agreed with the clinical experts.
System and economic issues	
If the recommendation by CDA-AMC is positive, jurisdictions would not be willing to pay more than the lowest price currently negotiated for an GnRH analogue.	This is a comment from the drug plans to inform pERC deliberations.

ADT = androgen deprivation therapy; CDA-AMC = Canada's Drug Agency; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GnRH = gonadotropin hormone-releasing hormone; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

The CDA-AMC clinical review was based on a summary of clinical evidence provided by the sponsor in accordance with the CDA-AMC tailored review process.

Description of Studies

A phase III, multicentre, single-arm, open-label pivotal study (FP01C-13-001) and a phase III, single-arm, open-label, safety extension study (FP01C-13-001-EX) were submitted by the sponsor and assessed by the CDA-AMC review team.

The FP01C-13-001 study (N = 137) evaluated the efficacy, safety, and pharmacokinetics of leuprolide mesylate in adult patients with histologically confirmed prostate carcinoma with a baseline morning serum testosterone level of greater than 150 ng/dL. Patients enrolled in the FP01C-13-001 trial were from 26 sites (no sites in Canada) and scheduled to receive a total of 2 doses of leuprolide mesylate with a 6-month interval. The primary objectives of the FP01C-13-001 trial included establishing the efficacy of leuprolide mesylate for up to 1 year, as measured by the percentage of patients with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) by day 28 plus or minus 1 day following the first injection of leuprolide mesylate and the percentage of patients with serum testosterone suppression (≤ 50 ng/dL) from day 28 through day 336 (remaining duration of the study); determining the safety and tolerability of leuprolide mesylate for up to 1 year of exposure; and evaluating the pharmacokinetic behaviour of serum leuprolide. The median age of the patients in the FP01C-13-001 trial was 71.0 years (range, 51 to 88). The race composition of the study population was 89.8% white, 5.8% Black or African American, 3.6% Asian, and 0.7% unknown. Approximately, 2.9% had stage I, 22.6.% had stage II, 27% had stage III, and 23.4% had stage IV prostate cancer, respectively; the disease stage in the remaining 24.1% of the study population was unknown.

The FP01C-13-001-EX study, conducted in [redacted] in the US, enrolled [redacted] who participated in the FP01C-13-001 pivotal study and assessed the safety and tolerability of leuprolide mesylate in these patients for up to 1 year.

Efficacy Results

Serum Testosterone Levels of 50 ng/dL or Less (Primary End Point)

In the FP01C-13-001 trial, serum testosterone level suppression to castrate levels (≤ 50 ng/dL) was reached by 98.5% (95% CI, 94.8% to 99.8%) of the ITT population by day 28 plus or minus 1 day following the first dose of leuprolide mesylate. By day 336, 97.0% (95% CI, 92.2% to 98.9%) of the ITT population achieved castrate testosterone levels (≤ 50 ng/dL).

The sponsor provided post hoc subgroup analyses, including subgroup results by disease stage and by disease characteristics at enrolment in the response to an information request by CDA-AMC seeking the sponsor's input on how to define advanced prostate cancer. Results from the subgroup analyses showed that in general, the proportion of patients who achieved castrate testosterone level (≤ 50 ng/dL) was similar across subgroups.

Pharmacokinetic Parameters (Primary End Point)

In the FP01C-13-001 trial, after the first and second doses of leuprolide mesylate, mean serum leuprolide concentrations reached the maximum observed serum concentration (C_{max}) of [redacted] (median time to the maximum serum concentration [T_{max}]), respectively. The mean values of observed serum concentration at 4 weeks postdosing (C_{wk4}), observed serum concentration at 6 months postdosing (C_{mon6}), area under the concentration time curve calculated using the linear up and log down trapezoidal method from time 0 to 4 weeks postdosing ($AUC_{0\ to\ 4wk}$), area under the concentration time curve calculated using the linear up and log down trapezoidal method from time 0 to 6 months postdosing ($AUC_{0\ to\ 6mon}$), and mean serum concentration within 6 months postdosing ($C_{avg(0\ to\ 6mon)}$) were [redacted], respectively, after the first dose of leuprolide mesylate. The mean values of C_{wk4}, C_{mon6}, $AUC_{0\ to\ 4wk}$, $AUC_{0\ to\ 6mon}$, and $C_{avg(0\ to\ 6mon)}$ were [redacted], respectively, after the second dose of leuprolide mesylate.

Postsuppression Excursion of Serum Testosterone Greater Than 50 ng/dL (Secondary End Point)

In the FP01C-13-001 trial, the proportion of patients exhibiting postsuppression excursions of serum testosterone (> 50 ng/dL), either through “breakthrough” (i.e., episodes unrelated to leuprolide mesylate dosing), or through the “acute-on-chronic” surge (i.e., related to the second dose of leuprolide mesylate) was examined. Overall, no postsuppression breakthrough effect other than acute-on-chronic surge was observed when administered with leuprolide mesylate during the study period. Two out of 137 patients did not reach the castrate testosterone level (≤ 50 ng/dL) by day 28. Two patients exhibited postsuppression excursions of serum testosterone (> 50 ng/dL) after the second dose of leuprolide mesylate between day 28 and day 336, but their serum testosterone returned to the castration levels on day 336.

Serum Testosterone Suppression of Less Than 20 ng/dL (Secondary End Point)

In the ITT population of the FP01C-13-001 trial, 69.3% and 95.9% of the patients achieved testosterone suppression of less than 20 ng/dL by day 28 and by day 336, respectively.

PSA Levels (Secondary End Point)

In the ITT population (N = 137) of the FP01C-13-001 trial, mean baseline of PSA level was [redacted], and it decreased to [redacted] on day 28. The mean PSA level was [redacted] on day 168 [redacted] on day 336.

Luteinizing Hormone Levels (Secondary End Point)

In the ITT population of the FP01C-13-001 trial, the mean luteinizing hormone level at baseline was [redacted]. The mean serum luteinizing hormone level was [redacted] on day 28, [redacted] on day 168, and [redacted] on day 336.

Quality of Life (Primary End Point)

In the ITT population (N = 137) of the FP01C-13-001 trial, approximately 68.6% (94 of 137) of patients felt satisfied (answered QoL questions with 0 delighted, 1 pleased, or 2 mostly satisfied) with their lives at current condition at baseline. On day 168, 129 patients answered QoL and approximately 69.7% (90 of 129) of patients felt satisfied. On day 336, 132 patients answered QoL and approximately 65.9% (87 of 132) felt satisfied.

Harms Results

FP01C-13-001 Study

In the pivotal FP01C-13-001 study, the median duration of follow-up was [redacted] and approximately [redacted] of the study population received both doses of leuprolide mesylate. The most common treatment emergent adverse event (TEAE) in the safety analysis set of the FP01C-13-001 study (N = 137) were hot flush (48.9%), followed by hypertension (14.6%), pain in extremity (9.5%), injection site pain (7.3%), arthralgia (6.6%), fatigue (6.6%), nocturia (5.8%), back pain (5.1%), and nasopharyngitis (5.1%). Serious adverse events (SAEs) occurred in [redacted] of the safety analysis set with injury, poisoning, and procedural complications [redacted] being the most frequent SAEs. There were [redacted] deaths: [redacted] due to stroke, [redacted] to metastatic prostate cancer and acute renal failure, and [redacted] unknown reasons. Five patients (3.6%) discontinued the study due to TEAEs, including acute kidney injury, atrial fibrillation, cerebrovascular accident, death, hormone-refractory prostate cancer, and metastatic prostate cancer.

FP01C-13-001-EX Study

In the extension study FP01C-13-001-EX ([redacted]), the median duration of follow-up was [redacted] (range, [redacted]). The most common TEAEs occurred during the extension period were acute kidney injury ([redacted]), increased blood triglycerides ([redacted]), dehydration ([redacted]), dizziness ([redacted]), fall ([redacted]), fatigue ([redacted]), and hypertension ([redacted]). Four patients ([redacted]) reported SAEs, and no discontinuation due to adverse events or deaths were reported during the extension period.

Critical Appraisal

Internal Validity

The evidence on leuprolide mesylate included in the sponsor's summary was based on 1 phase III, single-arm, open-label pivotal study (FP01C-13-001) and 1 phase III, single-arm, open-label, safety extension study (FP01C-13-001-EX). On the one hand, from a methodological perspective, the absence of an internal comparison group in the FP01C-13-001 pivotal study is a key limitation, which, due to the intrinsic nature of the single-arm design, leads to a low confidence in how well the findings could reflect the truth. Consequently, this makes inferences about the efficacy and safety of leuprolide mesylate challenging. On the other hand, from a regulatory perspective, it was considered acceptable for the pivotal FP01C-13-001 study to adopt the single-arm design as per the current FDA guidance for establishing the efficacy and safety of GnRH analogues for the treatment of advanced prostate cancer. Health Canada was in agreement with the FDA guidance that the single-arm study design was appropriate for the assessment of leuprolide mesylate.

The study design of the FP01C-13-001 trial was overall well-aligned with the FDA guidance by meeting major criteria outlined in the guidance.

The safety extension study, FP01C-13-001-EX, provided 2 additional doses of leuprolide mesylate approximately 6 months apart to the patients from the pivotal FP01C-13-001 study and assessed the safety of leuprolide mesylate for up to 2 years (i.e., including 1 year in FP01C-13-001 plus 1 year in the extension study). While all [redacted] received the first dose of leuprolide mesylate, it was noted that approximately [redacted] of the patients in the FP01C-13-001-EX study did not receive the second dose including [redacted] discontinued due to early termination unrelated to adverse events and [redacted] due to drug supply expiration. The large proportion of patients missing the second dose of treatment might result in a potential risk of underestimation of incidence of harms although the magnitude of the impact remained unknown.

A gap remains in the sponsor-submitted evidence due to the absence of direct or indirect evidence (i.e., the pivotal FP01C-13-001 study was single-arm), which limited the ability of the CDA-AMC review team to draw any evidence-based conclusion on the efficacy of leuprolide mesylate relative to other ADTs (including leuprolide products) currently available in Canada.

External Validity

The pivotal FP01C-13-001 study does not completely align with the population indicated in the Health Canada–approved indication in terms of advanced prostate cancer. The Health Canada–approved indication targets patients with advanced prostate cancer, while the pivotal FP01C-13-001 study did not limit the enrolment to patients with advanced prostate cancer but included patients with stage I to stage IV disease. Of note, according to the clinical experts consulted by the CDA-AMC review team, there is no universal definition for advanced prostate cancer; “patients with advanced prostate cancer,” as noted in the Health Canada–approved indication is subject to interpretation. The clinical experts consulted by the CDA-AMC review team noted that advanced prostate cancer commonly refers to biochemically recurrent and metastatic disease, yet patients with intermediate or high-risk localized prostate cancer can also be eligible for ADT. The sponsor, in their response to the information request by CDA-AMC, stated that “In clinical practice, the standard definition [of advanced prostate cancer] is disease that has progressed beyond localized treatment options, including locally advanced disease (e.g., T3 or T4 classification) that is not amenable to curative treatment, metastatic disease, and castration-resistant prostate cancer.” Treatment recommendations and guidelines for prostate cancer recognize that advanced prostate cancer encompasses both localized disease with high-risk features and metastatic disease and that all patients with advanced prostate cancer would typically require ADT. Nonetheless, both clinical experts consulted by the CDA-AMC review team agreed that the results generated from the FP01C-13-001 study population would still be generalizable to the Health Canada indicated population.

The clinical experts consulted by the CDA-AMC review team noted that the pivotal FP01C-13-001 study excluded patients who had an ECOG PS of greater than 2; those who received combination therapy with chemotherapy, immunotherapy, cryotherapy, radiotherapy, concomitant ADT, or GnRH therapy during study; and those who had a baseline morning serum testosterone level of 150 ng/dL or less, while the

Health Canada indication did not restrict the use of leuprolide mesylate in these patients. According to the clinical experts consulted by the CDA-AMC review team, these patients who were excluded from the FP01C-13-001 study would benefit from leuprolide mesylate treatment and account for a large proportion of patients with advanced prostate cancer. Nonetheless, the clinical experts felt that the results from the pivotal FP01C-13-001 study would still be generalizable to these patients.

Economic Evidence

Cost and Cost-Effectiveness

The sponsor submitted a cost comparison evaluating the annual drug and health care resource use costs associated with leuprolide mesylate compared to other available ADTs.

At the submitted price of $1,499.00 per 42 mg extended-release emulsion for injection, the annual drug acquisition cost of leuprolide mesylate is estimated to be $2,998 per patient. Based on publicly available list prices, the annual cost of leuprolide mesylate is expected to be lower than the associated annual cost of all ADTs (i.e., buserelin acetate, degarelix, goserelin acetate, leuprolide acetate [Eligard], leuprolide acetate [Lupron Depot], relugolix, and triptorelin). Compared with the 6-month ADT formulations (i.e., leuprolide acetate [Eligard] and triptorelin), leuprolide mesylate is estimated to be associated with cost savings of $322 annually when compared to 45 mg leuprolide acetate (Eligard) and 22.5 mg triptorelin. Incremental savings associated with leuprolide mesylate are based on publicly available list prices and may not reflect actual prices paid by drug plans.

The sponsor's cost comparison was associated with limitations including the uncertainty in the assumption of clinical similarity of leuprolide mesylate and other ADTs, the potential overestimation of administration costs, and not including 3.6 mg goserelin acetate as an ADT comparator. Leuprolide mesylate is priced lower than all ADT comparators and is cost saving at public list prices. All incremental costs or savings are based on publicly available list prices and may not reflect actual prices paid by public drug plans in Canada.

Budget Impact

CDA-AMC identified several key limitations in the sponsor's analysis:

- Uncertainty in the market uptake and market displacement of leuprolide mesylate.
- The patient population was likely underestimated and is associated with uncertainty.
- Reference scenario market shares and patient distribution of ADT formulations was uncertain and did not meet face validity.

CDA-AMC conducted reanalyses including the revision of the market uptake and market displacement based on the 2024 IQVIA Pharmastat database and displacement of market shares from 6-month ADT formulations; adjustment of the patient population; and revision of the reference scenario market shares. The CDA-AMC base case estimated that funding leuprolide mesylate for the treatment of advanced prostate

cancer would be associated with an incremental cost savings of $79,343 in year 1, $223,133 in year 2, and $416,255 in year 3 with a 3-year total of $718,731.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice-Chair), Dr. Philip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: May 14, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@cda-amc.ca.