



CADTH Reimbursement Recommendation

Relugolix (Orgovyx)

Indication: For the treatment of adult patients with advanced prostate cancer

Sponsor: Sumitomo Pharma Canada, Inc.

Final recommendation: Reimburse with conditions



Summary

What Is the CADTH Reimbursement Recommendation for Orgovyx?

CADTH recommends that relugolix (Orgovyx) should be reimbursed by public drug plans for the treatment of advanced prostate cancer if certain conditions are met.

Which Patients Are Eligible for Coverage?

Orgovyx should only be covered to treat adult patients who have advanced prostate cancer and are not candidates for chemotherapy or surgical therapy soon after initiating treatment.

What Are the Conditions for Reimbursement?

Orgovyx should only be reimbursed if it is prescribed by a clinician with expertise in managing prostate cancer. The cost of Orgovyx should not exceed the drug program cost of treatment with the least costly alternative treatment. Orgovyx should be stopped if the patient experiences severe side effects.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that Orgovyx resulted in the suppression of testosterone levels compared to leuprolide.

Orgovyx met some needs identified by patients, including being convenient to take, potentially delaying progression, and having manageable treatment side effects.

Based on CADTH's assessment of the health economic evidence, Orgovyx 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 higher cost for Orgovyx compared with other androgen deprivation therapies (ADTs), so the cost of Orgovyx should not exceed the drug program cost of treatment with the least costly ADT reimbursed for the treatment of advanced prostate cancer.

Based on public list prices, Orgovyx is estimated to result in slightly less than \$1,000,000 in cost savings to the public drug plans over the next 3 years. However, the actual budget impact is uncertain.

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



Summary

levels. It is estimated that 24,600 people in Canada were diagnosed with prostate cancer in 2022.

Unmet Needs in Advanced Prostate Cancer

For patients with advanced prostate cancer, there is a need for effective treatments that can delay disease progression and extend life while improving or maintaining the quality of life of patients. Patients also identified a need for treatments that could be easily administered and accessed.

How Much Does Orgovyx Cost?

Treatment with Orgovyx is expected to cost approximately \$3,303 per patient in year 1 and \$3,285 per patient in subsequent years.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that relugolix be reimbursed for the treatment of advanced prostate cancer in adult patients only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

One phase III, randomized, open-label, parallel-group, multicentre trial (HERO, N = 934) demonstrated that treatment with relugolix resulted in a higher suppression of testosterone levels compared to leuprolide. The study was conducted in adult patients who were candidates for at least 1 year of continuous ADT for various stages of advanced prostate cancer, including biochemical relapse, newly diagnosed androgen-sensitive metastatic disease, and advanced localized disease not suitable for primary surgical intervention. Specifically, from day 29 through week 49, the percentage of patients who achieved sustained testosterone suppression was 96.7% (95% confidence interval [CI], 94.9% to 97.9%) for those treated with relugolix compared to 88.8% (95% CI, 84.6% to 91.8%) for those treated with leuprolide, thus meeting the primary study objective with a prespecified noninferiority margin of -10% and demonstrating superiority (lower bound of 95% CI > 0; P < 0.0001). The mean difference between the treatment groups in the proportion of patients who achieved sustained testosterone suppression at week 49 was 7.9% (95% CI, 4.1% to 11.8%). From day 29 through week 49, a higher percentage of patients achieved and maintained profound castration levels of testosterone (< 20 ng/dL) with treatment with relugolix (81.6%; 95% CI, 78.1% to 84.5%) compared with those treated with leuprolide (68.6%; 95% CI, 63.0% to 73.5%), a level of suppression the clinical experts consulted by CADTH considered to be more important. However, the analysis for this outcome was outside the statistical hierarchy and was not adjusted for multiplicity.

pERC noted that the percentage of patients who experienced treatment-emergent adverse events in the HERO trial was similar for those treated with relugolix and those treated with leuprolide, and they considered the harms manageable and in line with clinical expectations for the ADTs.

Patient-identified needs included availability of treatments that can extend life, improve quality of life, delay disease progression, reduce side effects, be administered orally rather than by injection, and potentially more easily accessed. pERC concluded that relugolix met some of the needs identified by patients, such as potentially delaying progression, being convenient to take, and having manageable treatment side effects.

At the sponsor-submitted price for relugolix and the publicly listed prices for other ADTs, relugolix ranged from being similar to or potentially less costly than other ADTs. Although the phase III HERO trial showed relugolix was noninferior compared to leuprolide acetate, comparative efficacy and safety of relugolix versus other ADTs could not be determined. Therefore, the total drug cost of relugolix should not exceed the total drug cost of other ADTs.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults (18 years or older) with histologically or cytologically confirmed prostate cancer who are not candidates for chemotherapy or surgical therapy soon after initiating ADT.	Evidence from the HERO trial demonstrated that treatment with relugolix resulted in clinical benefit in terms of testosterone suppression, compared with leuprolide, in patients with advanced prostate cancer.	<p>The eligibility criteria for the HERO trial included patients with any of the following:</p> <ul style="list-style-type: none"> evidence of biochemical (PSA) or clinical relapse following local primary intervention newly diagnosed androgen-sensitive metastatic disease advanced localized disease unlikely to be cured by primary intervention with either surgery or radiation (this group included patients with localized or locally advanced disease with higher risk features). <p>pERC agreed with the clinical experts' feedback and stakeholders' feedback indicating that relugolix is appropriate for use as an ADT in the same patient population that injectable ADTs are currently used.</p>
2. Patients should have good performance status.	Patients with an ECOG performance status of 0 or 1 were included in the HERO trial.	pERC agreed with the clinical experts that patients with an ECOG performance status of 2 or 3 could potentially benefit from relugolix
Renewal		
3. Assessment for disease progression should be based on clinical, PSA, and radiographic evaluations at least every 3 to 6 months or per physician's discretion.	According to clinical expert input, in clinical practice, clinical and PSA assessments are conducted every 3 to 6 months.	—
Discontinuation		
4. Reimbursement of relugolix should continue until unacceptable toxicity.	Patients from the HERO trial discontinued treatment upon the development of unacceptable toxicity.	—
Prescribing		
5. Relugolix should be prescribed by a clinician with expertise in management of PC and ADT.	To ensure that relugolix is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. Relugolix pricing should be negotiated so that it does not exceed the drug program cost of treatment	Relugolix is considered noninferior compared to leuprolide acetate, but comparative efficacy and safety of	—

Reimbursement condition	Reason	Implementation guidance
with the least costly ADT reimbursed for the treatment of advanced PC.	relugolix versus other ADTs could not be determined. Therefore, there is insufficient evidence to justify a cost premium for relugolix over the least expensive ADT reimbursed for advanced PC.	
Feasibility of adoption		
7. The feasibility of adoption of relugolix must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen.

Discussion Points

- pERC considered the results of a sponsor-submitted indirect treatment comparison (ITC) comparing the efficacy and safety of relugolix versus other medical ADTs available in Canada. [REDACTED]. However, the committee noted the heterogeneity in the data within the network meta-analyses (NMAs) and acknowledged the clinical experts' observation that profound castration levels would have been a better efficacy outcome for the Canadian context. They also noted that the major adverse cardiac event (MACE) assessment was performed too early, hence the outcome was noninformative. pERC noted that relugolix, similar to the administration of other ADTs in clinical practice, should be used with caution in patients with MACEs.
- pERC noted that the HERO trial did not assess the effectiveness or safety of relugolix as part of an intensification therapy option or as neoadjuvant or adjuvant therapy to radiation therapy. The committee noted that the studies the sponsor submitted to fill the evidence gaps had several limitations (e.g., small phase I or phase II open-label studies, short duration) and insufficient evidence to draw definitive conclusions.
- pERC noted that despite relugolix's faster testosterone suppression and recovery profile compared to leuprolide (and degarelix in a phase II trial), evidence gaps remain, such as absence of a direct comparison with other ADTs besides leuprolide, limited evidence regarding the safety and effectiveness of relugolix when used in combination with other systemic anticancer therapies and/or radiation, and the use of outcomes with no proven reliability (depth of testosterone suppression) as surrogates for duration of clinical response, progression-free survival, or overall survival.
- pERC deliberated using relugolix as an adjuvant or neoadjuvant therapy with or without radiation in locally advanced settings where the treatment may be stopped after 18 months, and they noted a lack of evidence for sustained efficacy of oral relugolix compared to parenteral ADTs. In particular,

the committee noted that, unlike the parenteral ADTs which may confer many months of testosterone suppression after treatment, relugolix has a rapid testosterone recovery, which could reverse the efficacy gains of testosterone suppression.

- pERC discussed the need to highlight patient adherence with relugolix because the faster suppression and recovery profile of the drug suggest that patients could have a significant impact on their testosterone levels and treatment effects if they do not take the drug as prescribed.
- pERC discussed that patients in Ontario and the Eastern provinces may have additional costs, which may make oral relugolix less accessible through publicly funded programs, and it may require private coverage.
- The pricing condition is based on the assumption of equal effectiveness and safety between relugolix and other ADTs. There is insufficient evidence to base conclusions about the long-term comparative effectiveness and safety of relugolix versus other ADTs, and further price reductions may be warranted.

Background

Prostate cancer is a malignancy in which prostate cells grow uncontrollably, often driven by testosterone-producing pathways. In its early stages, prostate cancer may be asymptomatic or present with nonspecific symptoms such as altered urination patterns, blood in the urine or semen, painful urination and/or ejaculation, pelvic area pain, and erectile dysfunction. As the tumour grows or metastasizes, typically to bones in 90% of cases, symptoms such as bone pain or mobility issues can severely affect quality of life.

Prostate cancer spans various stages, from nonmetastatic, localized disease to castration-resistant metastatic prostate cancer. Advanced prostate cancer is a severe subset of prostate cancer with a high risk of progression or death, requiring ADT. It represents a broad range of incurable disease states, with diverse clinical options and survival times. Survival rates vary significantly, from nearly 100% over 5 years for localized and locally advanced prostate cancer to 34% for metastatic prostate cancer.

In Canada, prostate cancer is the most common cancer among men, with approximately 24,600 diagnoses in 2022. It is estimated that 1 in 8 people in Canada will develop prostate cancer in their lifetime. The prevalence was 0.66% in 2018 (calculated using prevalent cases and the adult male population at the time), and this rate is assumed to have remained stable into 2024, balancing out incidence and mortality rates.

Relugolix (Orgovyx) has been approved by Health Canada for advanced prostate cancer in adult patients. Relugolix (Orgovyx) is an ADT. It is available as a 120 mg oral tablet; the dosage recommended in the product monograph is a loading dose of 360 mg on the first day followed by 120 mg orally once daily.

Sources of Information Used by the Committee

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

- a review of 1 phase III, randomized, multicentre, open-label, parallel-group clinical study in adult patients with advanced prostate cancer
- patients' perspectives gathered by patient groups, The ADT Educational Program, the Canadian Cancer Society (CCS), and PROCURE
- input from public drug plans and cancer agencies that participate in the CADTH review process
- opinions from 2 clinical specialists with expertise diagnosing and treating patients with advanced prostate cancer
- input from 2 clinician groups, including The ADT Educational Program and the British Columbia Genitourinary Group with the Vancouver Prostate Centre
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from the clinical experts consulted by CADTH for the purpose of this review.

Patient Input

A total of 3 patient groups submitted 3 inputs. The ADT Educational Program supports patients living with prostate cancer undergoing hormone therapies (ADTs). The CCS is the only national charity that supports patients living with all types of cancer across the country with research, compassionate support system, and by engaging in establishing health policies. These patient groups were represented by 1 patient each in their submissions. The third patient group, PROCURE, is a charitable organization that educates, supports, and informs people affected by prostate cancer and promotes and contributes to financing research. PROCURE collected information from an online survey conducted in May 2022, in which 263 patients participated.

In The ADT Educational Program input, a patient living with advanced prostate cancer said he has been on ADT almost continuously for more than 20 years and has experienced many side effects. The patient, on behalf of other patients, stated that the most disturbing side effects are hot flashes, fatigue, and loss of sexual interest. In addition, he said patients also regularly experience loss of muscle mass yet gain weight as fat, making simple tasks such as walking upstairs difficult. Also, based on input, ADT affects memory, can lead to depression and insomnia, and make patients feel weak, old, flabby, and demoralized. He also stated that the depot injection form of ADT agents may cause inflammation at the injection site causing discomfort for days after injection. According to his input, some patients may delay getting repeated injections or take risky drug holidays just to avoid injections, which can cause their cancer to fulminate. PROCURE said some patients decide to opt for orchiectomy to avoid regular injections. Another patient from CCS stated that he

experienced side effects such as weight gain, impact on kidneys and liver, as well as reduced sexual desire, which the patient noted was a key side effect. In both inputs, the patients said taking ADT can cause side effects that may require other medications, such as antidepressants or a kidney-protective drug. The patient from CCS said he felt weak and tired, which reduced his motivation to exercise. The patient's wife said she did not feel a significant impact on her life apart from the limited sexual desire the patient felt as the side effect of treatment. According to the PROCURE input, patients and partners often mourn the loss of a satisfying sexual relationship, and advanced cancer creates anxiety within the couple. Also, PROCURE stated that children and family may experience anxiety if their parent passes away from the cancer, or that they may be at risk of getting prostate, breast, or ovarian cancers if their parent living with prostate cancer is a carrier of a *BRCA* mutation. PROCURE said that frequent travel to clinics or the hospital for medical follow-up exams can be costly with injection hormone therapy, and it takes too long (i.e., from months to years) for their testosterone levels to return to normal levels after ending long-term ADT.

Based on inputs, 1 of the key outcomes important to patients was safety of medication and minimizing side effects. Other key outcomes cited by patients to be important included maintaining long-term survival (with ADT) and good quality of life. PROCURE also stated that patients want improved outcomes in treatment, such as slowing down the progression of cancer, extending of life expectancy, and decreasing prostate-specific antigen (PSA) levels. All inputs indicated that patients living with prostate cancer would appreciate new treatment that is not as difficult or invasive and is a patient-friendly alternative form of ADT.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Despite advancements in prostate cancer treatment leading to longer overall survival, resistance to therapies is inevitable, and most patients will eventually succumb to the disease. All current ADT options effectively induce profound medical castration (testosterone suppression).

One gap in current ADT options is the lack of oral administration. The available injectable forms may not suit all patients, although, according to the clinical experts, there is no published evidence that has influenced the Canadian clinical practice regarding a preference for oral options or that injectables negatively impact compliance. Because patients with advanced prostate cancer typically visit their physicians semiannually, the current treatment regimen does not greatly burden the health care system. However, for patients in remote areas of Canada who find travel challenging, an oral ADT option could address this unmet need. Relugolix is positioned as a foundational ADT. It may be particularly beneficial for patients in remote locations, those who prefer oral medication, or those needing intermittent rather than continuous ADT (e.g., if intermittent ADT is attempted to minimize the adverse effects of medical castration by withdrawing treatment in patients who have responded to continuous ADT) due to its rapid testosterone and quality of life recovery.

The Canadian consensus statement recommends a castrate level threshold of 0.7 nmol/L or less for patients with metastatic castration-sensitive prostate cancer (MCSPC), along with androgen receptor axis-targeted therapy intensification. Response measures include prolonging overall survival, progression-free survival,

time to skeletal events, symptomatic deterioration, and castration resistance. For patients with clinical or biochemical relapse after curative local therapy, goals include achieving castrate levels of testosterone, extending overall and metastasis-free survival, and delaying castration resistance.

Discontinuation of ADT in the MCSPC setting is rare, except in cases of intolerable toxicities. In the high-risk curative setting, ADT might be stopped more frequently due to toxicities, and decisions are based on a risk-benefit analysis at that time. Most ADT toxicities are manageable. Relugolix is prescribed by specialist oncologists and self-administered orally by the patient.

Clinician Group Input

Two clinician groups, The ADT Educational Program and the British Columbia Genitourinary Group with the Vancouver Prostate Centre, contributed their insights on prostate cancer treatment, specifically focusing on the need for better-tolerated and more convenient treatment options that enhance compliance. These groups support the development of an oral formulation of LHRH (luteinizing hormone–releasing hormone) antagonist to overcome the disadvantages of injectable forms, such as injection site reactions, discomfort due to high dosage volume, and the need for travel to clinics.

The clinician groups highlighted the current unmet need in prostate cancer treatment: resistance to therapies due to androgen-independent mechanisms. They believe that an oral form of ADT would be particularly beneficial for patients living far from cancer centres. However, they caution that long-term ADT might lead to compliance issues or increased pill burden, especially when combined with other therapies. The goal for ideal prostate cancer treatment is cure, but for advanced stages that have spread beyond the gland, the objectives shift to suppressing androgen with fewer side effects or less invasive administration, prolonging survival, and improving quality of life. Other important therapy goals include prolonging time to skeletal-related events, symptomatic deterioration, and castration resistance.

Patients best suited for relugolix include those with hormone-sensitive disease, newly diagnosed or substantial metastatic disease requiring prompt androgen suppression, patients needing short-term ADT, and those having difficulty accessing injection clinics. Additionally, it is beneficial for those preferring oral medication or needing intermittent ADT.

Response to relugolix is measured via serum PSA or imaging, similar to current ADT agents. For relugolix monotherapy, a “profound castration” level of testosterone (≤ 0.7 nm/L) is indicative of a pharmacologic effect. Generally, ADT is continuous and indefinite for patients with metastatic, locally advanced, or castrate-resistant prostate cancer, unless contraindications or intolerable side effects arise. Relugolix can also be administered intermittently based on serum PSA levels or for a fixed duration in patients receiving ADT with curative-intent radiation.

Urologists, medical or urologic oncologists, and radiation oncologists experienced in managing advanced prostate cancer should prescribe and monitor relugolix treatment. The medication can be dispensed in an outpatient setting, and patients take relugolix orally at home.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for Orgovyx:

- considerations regarding relevant comparators
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- potential need for a provisional funding algorithm.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Advice from CADTH
Relevant comparators	
Relevant comparators funded in most jurisdictions include leuprolide (comparator in the HERO trial), degarelix, buserelin, and goserelin, all of which are injectables.	This was a comment from the drug programs to inform pERC deliberations.
The primary efficacy outcome measure was medical castration rate, defined as achieving and maintaining serum testosterone suppression to castrate levels (< 50 ng/dL) by day 29 through 48 weeks of treatment. Other key secondary end points included castration rates on days 4 and 15, castration rates with testosterone < 20 ng/dL at day 15, and PSA response rate at day 15, and FSH level at day 176 (week 25, day 1). In clinical practice, what is the most appropriate frequency to determine treatment response?	Clinical experts consulted by CADTH reported that, currently, most patients with advanced prostate cancer would visit their physicians at least twice a year for review of disease control, symptoms, and toxicity management. In the management of MCSPC, the Canadian consensus statement recommends maintaining testosterone levels at or below 0.7 nmol/L, aligning with the “profound” castration level proposed by the drug sponsor. In addition, patient treatment in this context should be intensified with ARAT. According to the clinical experts, PSA levels and clinical end points are primarily used to assess clinical response. pERC agreed with the clinical expert regarding the relevant end points and the frequency of clinical assessment.
Patients in the HERO trial with disease progression during the treatment period were encouraged to remain on study and, if indicated, may have received radiotherapy as prescribed by the investigator. If patients had PSA progression (i.e., CRPC), they were allowed to receive enzalutamide or docetaxel during the study. What are the discontinuation criteria for relugolix?	The clinical experts noted that ADT is rarely ceased in the MCSPC and CRPC setting unless toxicities are truly intolerable. They also reported that, in the high-risk curative setting, ADT may be ceased due to toxicities more often; however, it is a balanced discussion based on risks and benefits at that time point. According to the clinical experts, most toxicities from ADTs are manageable. pERC agreed with the clinical experts that the attending physician should use clinical judgment regarding the discontinuation of therapy.
Considerations for prescribing of therapy	
Relugolix should be initiated with a loading dose of 360 mg (3 tablets) on the first day and continued with a 120 mg	This was a comment from the drug programs to inform pERC deliberations.

Implementation issues	Advice from CADTH
<p>tablet taken once daily at approximately the same time each day.</p>	
Generalizability	
<p>Can the trial results be generalized to patients with ECOG performance status > 1?</p>	<p>The clinical experts agree that the results are generalizable to patients with ECOG performance status > 1. pERC agreed with the clinical experts, noting that patients with an ECOG performance status of > 1 may be eligible for the treatment with relugolix, at the discretion of the treating clinician.</p>
Funding algorithm (oncology only)	
<p>Under what clinical circumstances would relugolix be used over existing agents?</p>	<p>The clinical experts noted that patient preference for oral treatment or preference for rapid return of testosterone to normal levels upon cessation of drug may be factors for using relugolix over existing agents. pERC agreed with the clinical experts that choice of relugolix over other treatments can be made in case of patient preference for oral treatment or preference for rapid return of testosterone to normal levels upon drug cessation.</p>
Care provision issues	
<p>Relugolix has the potential for drug-drug and drug-laboratory interactions, requiring assessment and/or intervention. Would this limit its use in combination regimens (i.e., apalutamide is a strong CYP3A4/P-gp inducer, and abiraterone was a prohibited medication in the trial)?</p>	<p>The study did not include abiraterone and apalutamide, which are significant intensification options in this therapeutic area. The sponsor proposed a comprehensive listing for the use of relugolix in combination with all ARATs. However, it may be appropriate to consider restricting combination partners to those explicitly included in the study, such as the use of enzalutamide specifically in the context of metastatic castration-resistant prostate cancer, as suggested by the clinical experts. pERC agreed with the clinical experts and noted the limited evidence on efficacy of relugolix as part of an intensification therapy or in combination with radiation therapy for advanced prostate cancer. In the absence of definitive evidence about the clinical benefit or safety of using relugolix in combination with ARATs, pERC suggests that using relugolix as part of an intensification strategy should be based on the professional judgment of the prescribing clinician. Drug-drug interactions with other systemic therapy should be reviewed carefully.</p>

ADT = androgen deprivation therapy; ARAT = androgen receptor axis-targeted therapy; CRPC = castration-resistant prostate cancer; CYP3A4/P-gp = cytochrome P450 3A4 and P-glycoprotein; ECOG = Eastern Cooperative Oncology Group; FSH = follicle-stimulating hormone; MCSPC = metastatic castration-sensitive prostate cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PSA = prostate-specific antigen.

Clinical Evidence

Systematic Review

Description of Studies

The HERO trial was a phase III, randomized, multicentre, open-label, parallel-group study conducted across 160 sites in 22 countries. The trial enrolled patients from April 2017 to October 2019 for the primary analysis and until August 2020 for the final analysis. A total of 934 patients were included in the primary analysis, with this number increasing to 1,078 in the final analysis. Patients were divided into 2 groups: 624 received relugolix and 310 received leuprolide in the primary analysis. Eligible participants were adult males with histologically or cytologically confirmed prostate cancer, candidates for at least 1 year of continuous ADT, and meeting specific criteria such as evidence of biochemical or clinical relapse, newly diagnosed androgen-sensitive metastatic disease, or advanced localized disease. Exclusions included a likely need for chemotherapy or surgical therapy soon after ADT initiation, prior extensive ADT or systemic cytotoxic treatment, brain metastases, recent significant cardiac events, conduction system abnormalities, and uncontrolled hypertension.

The intervention consisted of administering relugolix as a 120 mg tablet daily following a 360 mg oral loading dose on day 1, compared to leuprolide given as 22.5 mg 3-month depot injections every 12 weeks, both for a duration of 48 weeks. The study was structured into a 28-day screening phase, a 48-week treatment phase, and a follow-up phase of 30 days for safety and up to 90 days for assessing testosterone recovery. The primary end point was the sustained castration rate from week 5 to week 49. Secondary efficacy end points included sustained castration rate, profound castration rate, PSA response rate, FSH (follicle-stimulating hormone) level, castration recurrence-free survival for patients with or without metastatic cancer (final analysis), and testosterone recovery rate. Other end points assessed changes in quality of life, serum concentrations of various hormones, and safety end points like treatment-emergent adverse events, MACEs, clinical laboratory tests, vital signs, and electrocardiograms. Exploratory end points included overall survival and the presence of polymorphisms in germline genes.

The age distribution was similar between the 2 groups, with approximately 71% of patients in both groups aged 75 years or younger. The mean age was approximately 71 years, with a slightly higher median age in the relugolix group (72 years) compared to the leuprolide group (71 years). Ethnicity and race distributions were broadly comparable across both groups, with the majority being non-Hispanic or Latino and white. The study included participants from various geographic regions, with the largest proportion from Europe (approximately 40% in both groups), followed by North America, Asia, and other regions.

Clinically, approximately half of the participants in both groups presented with evidence of biochemical or clinical relapse following local primary intervention with curative intent. Newly diagnosed androgen-sensitive metastatic disease and advanced localized disease not suitable for primary surgical intervention were other major disease presentations. The distribution of disease stages at study entry was similar across both groups; approximately 32% had metastatic, 30% had locally advanced, and 29% had localized disease. Gleason scores were also similar, with the most common being 7 and 8 to 10. The majority of participants

had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Prior ADT and radiation therapy histories were noted in both groups, with a slightly higher numerical percentage of prior ADTs in the relugolix group. Cardiovascular risk factors were prevalent in more than 90% of participants in both groups, with a notable proportion also having lifestyle risk factors and a history of MACE.

Efficacy Results

The proportion of patients who achieved sustained testosterone suppression was 96.7% (95% CI, 94.9% to 97.9%) in the relugolix treatment group compared with 88.8% (95% CI, 84.6% to 91.8%) in the leuprolide group, with a mean difference between the relugolix and leuprolide treatment groups of 7.9% (95% CI, 4.1% to 11.8%). These results demonstrated noninferiority of relugolix compared to leuprolide (the lower bound of the 95% CI for the difference between groups was greater than the prespecified noninferiority margin of -10%; $P < 0.0001$), and also statistical superiority of relugolix compared with leuprolide (lower bound of the 95% CI > 0 ; $P < 0.0001$).

Patients in the relugolix group had a shorter time to achieve castration compared to those in the leuprolide group at profound castration levels of testosterone (< 20 ng/dL). The median time to profound castration was 15 days in the relugolix group compared with 29 days in the leuprolide group. At day 15, the difference in the proportion of patients achieving profound castration was more pronounced in the relugolix group (78.38%) compared with the leuprolide group (0.98%), with a statistically significant difference of 77.41% (95% CI, 73.98% to 80.83%; $P < 0.0001$).

Treatment with relugolix resulted in a higher proportion of patients achieving and maintaining profound castration (81.6%; 95% CI, 78.1% to 84.5%) compared with the leuprolide group (68.6%; 95% CI, 63.0% to 73.5%) from day 29 through 48 weeks, with a difference between groups of 13.0%.

Harms Results

Overall, the safety profile of relugolix suggests a profile that is consistent with the safety profile of the ADT therapeutic class. In the HERO trial, adverse events (AEs) were reported by a similar proportion of patients in both the relugolix (92.9%) and leuprolide (93.5%) groups. The most common AE for both groups was hot flush, occurring in more than half of the patients. Gastrointestinal issues such as constipation and diarrhea were more frequently reported in the relugolix group. All cases of constipation and diarrhea were mild to moderate, with only 1 patient withdrawing from the study due to these AEs. Serious adverse events (SAEs) were slightly numerically less common in the relugolix group (12.2%) compared to the leuprolide group (15.3%). The SAEs in the relugolix group included myocardial infarction (0.8%), acute kidney injury (0.6%), and urinary tract infections (0.5%). Within the leuprolide group, SAEs included anemia (1.0%), cardiorespiratory arrest (1.0%), and urinary tract infection (0.6%); grade 3 or 4 SAEs were slightly numerically more common in the leuprolide group.

Treatment discontinuation due to AEs was higher in the relugolix group (3.5%) compared to the leuprolide group (0.3%). The deaths reported were slightly numerically higher in the leuprolide group (2.9%) than in the relugolix group (1.1%), with cardiovascular-related deaths being more common in the leuprolide group. Vasomotor symptoms such as hot flushes and fatigue were common in both groups (56.1% in relugolix,

54.9% in leuprolide), but hepatic transaminase elevations were numerically higher in the relugolix group (7.6%) compared to the leuprolide group (5.5%). The incidence of MACEs was numerically higher in the leuprolide group. Loss of bone mineral density was reported in similar proportions in both groups; there were no significant liver-related toxicities meeting Hy's law criteria in either group.

Critical Appraisal

The HERO study, a phase III trial comparing relugolix with leuprolide in patients with advanced prostate cancer, demonstrated a robust methodology in terms of randomization, stratification, and sample size. Its open-label design, although potentially introducing bias, was mitigated by the objective nature of the primary outcome. The sensitivity analyses for the primary outcome and the approach to handling missing data enhance the study's robustness.

The applicability of the HERO study to typical Canadian practice may be limited due to several factors, including its lack of a clear definition of what constitutes locally advanced disease in the inclusion criteria and patient population. The study's focus on biomarkers such as testosterone and PSA, although relevant for advanced prostate cancer, does not fully capture the clinical outcomes of the disease. The study also does not address the combination of ADT with other systemic therapies nor does it inform on relugolix's use in patients undergoing radiation therapy. In addition, several additional standard-of-care medicines (available and reimbursed) in Canada that would ordinarily be combined with relugolix if it was approved in the MCSPC setting – abiraterone, enzalutamide, and apalutamide – were not permitted to be given concurrently in the HERO study. This raises concerns because of the potential use of relugolix in the MCSPC setting.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- sustained castration rate
- profound castration rate
- MACE
- loss of bone mineral density.

Table 3: Summary of Findings for Relugolix Versus Leuprolide for Patients With Advanced Prostate Cancer

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Leuprolide (N = 308)	Relugolix (N = 622)	Difference		
Sustained castration rate							
Sustained castration rate (< 50 ng/dL) Follow-up: from day 29 to day 337	930 (1 RCT)	HR = 0.2621 (0.1489 to 0.4613)	88.8 per 100 persons	96.7 per 100 persons (94.9 to 97.9)	7.9 more persons per 100 (4.1 to 11.8)	High ^a	Relugolix likely results in an increase in the number of patients with sustained castration compared to leuprolide.
Profound castration rate							
Profound castration rate (< 20 ng/dL) Follow-up: day 15	930 (1 RCT)	NR	0.98 per 100 persons	78.38 per 100 persons (75.06 to 81.53)	77.41 more persons per 100 (73.98 to 80.83)	High ^b	Relugolix results in an increase in the number of patients with profound castration at day 15 compared to leuprolide.
Cumulative probability of profound castration rate (< 20 ng/dL) Follow-up: day 29 to day 337	930 (1 RCT)	NR	68.6 per 100 persons	81.6 per 100 persons (78.1 to 84.5)	13.0 more persons per 100 (6.9 to 19.1)	High ^b	Relugolix results in an increase in the number of patients with profound castration compared to leuprolide.
Harms							
MACE Follow-up: day 337	930 (1 RCT)	NR	6.2 per 100 persons	2.9 per 100 persons (NR)	NR	Very low ^c	The evidence is very uncertain about the effects of relugolix compared to leuprolide on MACE.
Loss of bone mineral density Follow-up: day 337	930 (1 RCT)	NR	3.9 per 100 persons	3.2 per 100 persons (NR)	NR	Very low ^c	The evidence is very uncertain about the effects of relugolix compared to leuprolide on loss of bone mineral density.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event; NR = not reported; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aNo published between-group minimal important difference (MID) was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects; therefore, the null was used. Did not rate down for imprecision; a between-group difference of larger than the null and a CI that excludes the null suggest benefit compared to leuprolide as judged by the CADTH review team.

^aNo published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects, therefore the null was used. Did not rate down for imprecision; a between-group difference of larger than the null and a CI that excludes the null suggest benefit compared to leuprolide as judged by the CADTH review team.

^cRated down 2 levels for very serious concerns about imprecision due to very small number of events. Rated down 1 level for serious indirectness due to insufficient duration of follow-up for the outcome according to clinical expert input.

Source: Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

None submitted.

Indirect Comparisons

Description of Studies

The sponsor submitted an ITC designed to assess the efficacy and safety of relugolix compared to other medical ADTs available in Canada for adult male patients with advanced prostate cancer. The analysis included an NMA of RCTs identified from a systematic literature search that reported on testosterone suppression to castration levels and MACE outcomes at a 12-month (± 3 months) time point. The quality assessment of these RCTs utilized the Cochrane Risk of Bias tool. The NMA used a Bayesian framework, employing various models to estimate treatment effects for each outcome. Model fit assessment relied on the deviance information criterion, resulting in the selection of the random effects with informed prior model for testosterone castration and random-effects model with vague priors model for MACE as the primary analysis. An additional hierarchical approach was adopted, accounting for treatment class exchangeability and assuming normal distribution around class-specific means. Statistical heterogeneity was evaluated using the I^2 statistic. Sensitivity analyses were conducted using different models and priors.

Efficacy Results

The NMA included 7 studies for testosterone suppression, defined as sustained chemical castration with testosterone levels lower than 50 ng/dL at 12 months (± 3 months). [REDACTED]

Harms Results

The NMA included 4 studies for MACE, primarily comparing relugolix to degarelix and leuprolide. [REDACTED]

Critical Appraisal

Various limitations of the ITC were noted, including the heterogeneity in study characteristics and patient populations. The exploration of between-study differences and potential biases was further limited by incomplete data in the published trials included in the networks. Clinical experts consulted for this CADTH review noted imbalances in certain prognostic factors and effect modifiers (baseline testosterone concentrations, metastatic status of participants, previous hormonal treatment), which raises concerns for bias in the comparisons in the NMA. The clinical experts noted that in the Canadian clinical practice MACE assessment occurs later than 12 months (± 3 months) and that profound castration levels (< 20 ng/dL) would have been a more appropriate outcome measure, thus presenting notable generalizability issues. Considering these limitations, there is a high risk of bias in the comparison in this NMA, and the direction of that bias is unclear; hence, the findings of the sponsor-submitted ITC remain highly uncertain.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

The clinical evaluation of relugolix in advanced prostate cancer treatment encompassed 3 key studies. The phase II, open-label C27300 study focused on comparing relugolix with degarelix in patients with intermediate-risk localized prostate cancer, specifically assessing its role in neoadjuvant or adjuvant therapy with external beam radiation therapy. The phase I, open-label MVT-601-049 study investigated the combination of relugolix with abiraterone or apalutamide in patients diagnosed with either metastatic castration-sensitive or castration-resistant prostate cancer. The phase II, open-label Apa-RP study evaluated the efficacy of ADT in combination with apalutamide in patients who were treatment naive after radical prostatectomy, particularly those at high risk of metastases.

Efficacy Results

The C27300 study enrolled 103 patients, with 65 receiving relugolix and 38 receiving degarelix. The study showed relugolix achieved a sustained castration rate of 95% and a profound castration rate of 82% by 24 weeks. In comparison, degarelix showed a sustained castration rate of 89% and a profound castration rate of 68% by 24 weeks. The MVT-601-049 study included 25 patients, and demonstrated consistent testosterone suppression in combinations of relugolix with either abiraterone or apalutamide for 12 weeks treatment. The Apa-RP study, with 108 patients in the main study and 12 in the substudy, revealed a 100% sustained castration rate in both the substudy for 28 days and main study after 1 year.

Harms Results

In the C27300 study, the most common AEs were hot flushes (57%), fatigue (26%), and diarrhea (18%) in relugolix cohort. Deterioration in quality of life during treatment followed by improving health-related quality of life post treatment was noted when assessed with European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and QLQ-PR25. The MVT-601-049 study part 1 reported common AEs, including pain in extremity (20%), increased alanine transaminase (13.3%), and anemia (13.3%), with 1 SAE (6.7%) reported for a left femur fracture in the relugolix-abiraterone cohort (n = 15). The Apa-RP study identified hot flushes (50%) as the most common AE in the relugolix cohort (n = 12), with no significant SAEs or treatment discontinuations due to AEs reported.

Critical Appraisal

The internal validity of these studies is limited due to their open-label nature and the absence of true comparators. This design potentially biases the reporting of AEs, which are typically reported by patients whose responses may be subjective. Furthermore, the objectives of phase I and phase II clinical trials are limited in terms of establishing causal inference. The study durations also may not be long enough to assess long-term outcomes, particularly MACEs, which were identified by the clinical experts as notable AEs in patients with advanced prostate cancer. Externally, the studies' applicability to the Canadian context is questionable because none of the study sites were located in Canada. In addition, patients with cardiovascular diseases, a common comorbidity in the patient population with advanced prostate cancer, were excluded.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of evaluation	Cost-minimization analysis
Target population	Adult patients with advanced prostate cancer
Treatment	Relugolix
Dose regimen	360 mg once (loading dose) then 120 mg once daily (maintenance dose)
Submitted price	Relugolix: \$9.00 per 120 mg oral tablet
Treatment cost	\$3,303 in year 1; \$3,285 in subsequent years
Comparators	ADTs include: <ul style="list-style-type: none"> • buserelin • degarelix • goserelin acetate • leuprolide acetate • triptorelin
Perspective	Canadian publicly funded health care payer
Time horizon	Undefined (year 1 and subsequent year)
Key data sources	Key assumption of equal treatment efficacy and safety of relugolix based on: <ul style="list-style-type: none"> • phase III noninferiority HERO trial comparing relugolix to leuprolide acetate • sponsor-commissioned indirect treatment comparison comparing relugolix to selected ADTs (degarelix, leuprolide acetate, triptorelin, and goserelin acetate).
Costs considered	Drug acquisition costs
Key limitations	<ul style="list-style-type: none"> • The assumption of clinical similarity between relugolix and other ADTs is uncertain due to limitations with the sponsored indirect treatment comparison and the limited duration of the pivotal noninferiority trial. • Cost savings associated with relugolix are highly variable depending on the ADT received as well as the choice of dosing form. The largest estimated cost savings are relative to buserelin, which is not commonly used in clinical practice (0.03%) which was confirmed by clinical expert feedback consulted by CADTH. The cost savings of relugolix relative to the most commonly used ADT forms (leuprolide acetate [Eligard], 45 mg and 22.5 mg) are highly uncertain. • Confidential pricing agreements for comparators (ADTs) are unknown.
CADTH reanalysis results	<ul style="list-style-type: none"> • CADTH did not conduct reanalyses for the base case. Uncertainty in the comparative clinical effects and whether relugolix is similar to other ADTs could not be addressed. • CADTH conducted additional scenario analyses where the drug costs of relugolix were compared to the most commonly used ADT in clinical practice and its most frequently used drug formulations (leuprolide acetate [Eligard], 45 mg and 22.5 mg). Across these scenarios, the cost differences ranged from an added cost of \$13 per patient in year 1 to cost savings of \$279 per patient in subsequent years of treatment. • The extent of (and whether there is) cost savings associated with relugolix compared to other ADTs is highly dependent on the specific comparator(s) and the dosing form(s) used in each jurisdiction, as well as their specific confidential negotiated prices.

ADT = androgen deprivation therapy.



Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The sponsor's prevalence-based approach to estimate the target population was uncertain. The clinical experts indicated that an incidence-based approach is more clinically relevant (i.e., only incident patients would likely be considered for treatment with relugolix) and that the sponsor's derivation of patients with localized prostate cancer eligible for treatment did not meet face validity.
- The market shares of relugolix may be overestimated based on its anticipated use in clinical practice, shorter duration of testosterone suppression compared to currently used ADTs, and patient preference for less frequent administrations. The market uptake of relugolix would likely not surpass those of degarelix according to clinical experts consulted by CADTH.
- The price of drugs paid by public plans is uncertain because confidential pricing is likely in place.

The CADTH reanalysis estimated that the budget impact of reimbursing relugolix for the treatment of adult patients with advanced prostate cancer would result in cost savings to the drug plans of \$864,382 across 3 years. CADTH conducted scenario analyses to address remaining uncertainty. Based on these results, CADTH found that the drug expenditure of relugolix is highly sensitive to the size of the eligible population and predicted market uptake. Estimates from these scenario analyses ranged from cost savings of \$220,627 to \$6,548,612 based on public list prices.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: April 10, 2024

Regrets: Three expert committee member(s) did not attend.

Conflicts of interest: None.

Minor reconsideration pERC subpanel meeting date: July 9, 2024



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