CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

relugolix (Orgovyx)

(Sumitomo Pharma Canada, Inc.)

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

November 27, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Group Input

PROCURE Website

1.About Your Patient Group

Founded in 2003, PROCURE is a charitable organization in the fight against prostate cancer. It educates, supports, and informs people affected by this disease. It promotes and contributes to the financing of world-class research.

Our services include: Our full range of free support and information services aims to help people affected by prostate cancer and their loved ones. We offer quick access to healthcare professionals specialized in uro-oncology available 7 days a week via a toll-free support line as well as comprehensive information tools and a variety of resources to help individuals affected by prostate cancer, including caregivers, employers, the public and healthcare professionals, better understand the disease and treatment options.

We raise awareness: We organize a variety of events throughout the year to raise awareness about prostate cancer. The funds we raise during these activities allow us to pursue our mission to help people affected by this disease and to fund world-class research projects.

We advance research: We are fully committed to prostate cancer research, and we play an essential role in its advancement by providing biospecimens and data of high scientific value from our PROCURE Biobank. We are doing everything we can to better understand this disease, diagnose it earlier and treat it in a targeted and precise manner.

2.Information Gathering

Analysis of patient calls to our specialized uro-oncology healthcare professionals through our toll-free line. Cohort of 3,500+ patients with localized, locally advanced, metastatic, recurrent, hormone-sensitive, or castration-resistant prostate cancer with or without metastasis. In addition to distress and treatment choices, the rising PSA level post-treatment, recurrence, hormone therapy and its side effects, and metastases are the main concerns of incoming patient calls. For such calls, more than 60 minutes are usually required, along with periodic follow-ups.

In 2022 and 2023, 17% of our interventions were and are associated with advanced prostate cancer. A significant portion of these interventions involves questions directly related to side effects of hormone therapy and injection procedures and local side effects.

PROCURE’s surveys

In May 2022, in collaboration with the Leger firm, PROCURE conducted an online Canadian survey on the quality of life of our patients treated for prostate cancer, in which 263 patients participated. According to this survey, the main challenges posed by treatment in 50% of respondent included managing side effects, living with uncertainty, and maintaining a positive attitude.

In March 2018, PROCURE conducted an online Quebec survey on patient’s needs of our patients treated with advanced prostate cancer. In response to the question: What do you hope for from future treatments for prostate cancer?

- Slows down the progression of cancer: 95%
- Extends life expectancy: 94%
- Improves the quality of life: 98%
- Helps manage or diminish side effects: 93%
- Decreases PSA levels: 91%

3.Disease Experience

There are several types of prostate cancer: those that progress slowly (low risk), those with an intermediate risk of progression (low or high), those at high risk and very high risk of progression, and those that are aggressive. Prostate cancer is a highly complex disease. Like other types of cancers, this illness affects not only the patient but also their partner and family.

No patient receives an initial diagnosis of metastatic castration-resistant prostate cancer (mCRPC). Therefore, the side effects described below are often related to the initial treatment or a combination of treatments, which may include surgery, radiotherapy, and hormone therapy, among others.

Erectile dysfunction, dry orgasms, loss of libido, and incontinence have a direct impact on partners. The shock is undeniable. Patients and their partners must redefine their priorities and learn to live differently.

Partners unintentionally become caregivers. This role is demanding, accompanied by stress, anxiety, and resulting depression. They often have to mourn the loss of a satisfying sexual relationship. The same goes for intimate relationships: the loss of libido, fatigue, and changes in masculine characteristics often lead the man to avoid any intimate relationship with his partner. The consequences are significant.

Advanced cancer creates anxiety within the couple, not knowing how much time they have ahead of them, in addition to having to manage the side effects of treatments. On the family level, children become at risk for the rest of their lives. If the cancer is aggressive and fatal, they will have to mourn their father at a young age.

If their father carries a BRCA genetic mutation and has prostate cancer, both boys and girls have an increased risk of developing certain types of cancers, such as prostate cancer, breast cancer, and ovarian cancer, if they inherit the altered gene.

That's why genetic assessment and regular medical follow-up are essential to detect and treat any signs of the disease early, and appropriate preventive measures can be considered based on each child's individual risk.

In addition, there is the anxiety that children may feel, given the family context and the concern about their own risk of developing cancer.

Experiences With Currently Available Treatments

Patients: They particularly struggle to comprehend when their specialist expresses a statement like "if I had to choose a cancer, prostate cancer would be at the top of my list." It's a complex cancer, especially when it has breached the capsule or is at an advanced stage.

The side effects related to standard hormone therapy are significant and challenging for many, especially when taken over the long term. Injections are often a source of pain at the injection site. Frequency of travel to clinics or hospital for medical follow up exams and/or hormone injections such as leuprolide (Lupron, Lupron Depot, Eligard), waiting time, gas, parking fees or public transportation (taxis, bus, etc.) can take its tole. The exacerbation of their side effects with a change or addition of a new treatment is one of the expressed concerns.

In addition:

Being scared of injections: Many patients are scared of injections. Not only do they have to deal with their prostate cancer treatment, but injections can also be a source of pain or anxiety from call we are receiving. As a matter of fact, some of our patients decided to opt for orchiectomy in order to avoid injections on a regular basis.

Nurses - Management of injections and stress: Not all nurses are adequately trained to administer hormone therapy treatments to patients. Stress is associated with injections, including:

1. Preparing and planning the injections
2. Ensuring the proper mixture
3. Ensuring proper site administration
4. Dealing with patient questions that they cannot answer
5. Addressing patient complaints about pain
6. Handling patient non-compliance (no-shows)

Testosterone and side effects: Based on calls from our patients, we know well that the return to normal testosterone levels once the treatment is stopped is very slow. Some patients, especially the elderly **and** those who have used androgen deprivation therapy for a long time, do not see their testosterone levels return to normal for several months, or even several years, after the end of their treatment.

Quality of life: For many patients, access to professionals such as sexologists, psychologists, physiotherapists, or kinesiologists is either non-existent, too expensive, or the waiting time is too long. Many of them have never met their care team except for their treating physician. Few have comprehensive information or answers to their questions to manage their expectations.

4.Improved Outcomes

As mentioned above, response to the question *What do you hope for from future treatments for prostate cancer?*

- Slows down the progression of cancer: 95%
- Extends life expectancy: 94%
- Improves the quality of life: 98%
- Helps manage or diminish side effects: 93%
- Decreases PSA levels: 91%

5.Experience With Drug Under Review

We have not had access to patients who participated in the HERO Phase 3 clinical trial for this evaluation. We have, however reviewed positions that are in the public domain for ORGOVYX® (relugolix):

Health Canada approves ORGOVYX® (relugolix) for advanced prostate cancer (Ontario, October 23, 2023)

- The approval is based on efficacy and safety data from the Phase 3 HERO study of ORGOVYX in men with advanced prostate cancer. ORGOVYX is expected to be available for prescription in Canada in Q1 2024.
- ORGOVYX was previously approved by the U.S. Food and Drug Administration in 2020 and granted marketing authorization by the European Commission for advanced hormone-sensitive prostate cancer in 2022.

OncLive: Relugolix Wins Approval in Canada for Advanced Prostate Cancer (October 23, 2023)

FDA approves relugolix for advanced prostate cancer (2020)

NIH National Cancer Institute: Relugolix Approval Expected to Alter Treatment for Advanced Prostate Cancer (2021)

European Medicines Agency (2022)

EPAR/Orgovyx

Orgovyx EPAR Public Assessment Report

Last updated on July 18, 2023

- The European Medicines Agency decided that Orgovyx benefits are greater than its risks and it can be authorised for use in the EU.
- A main study showed that Orgovyx was as effective as standard treatment with another medicine (leuprorelin) in reducing testosterone levels of patients with advanced hormone-sensitive prostate cancer. Orgovyx was generally well-tolerated by most of the patients. Its side effects were mild and manageable.

HAS – Haute Autorité de Santé, France – Orgovyx summary (2023)

Adopted by the Transparency Committee on 26 April 2023

- Favourable opinion for reimbursement in the “treatment of adult patients with advanced hormone sensitive prostate cancer”

It has been stated in scientific literature that the potential benefits of a daily-dosed oral agent could be multiple: (1) offers a more patient-friendly alternative with limited health care provider visits or procedures and no risk of local site reactions; (2) allows more flexible dosing and an option for prompt cessation of treatment due to intolerance or treatment-related side effects; and (3) eliminates the need for a lead-in antiandrogen to counteract potential testosterone flare induced with LHRH agonist-based treatments (such as Casodex) (Sachdev et al. Eur Urol. 2020).

Based of the HERO Study Results
In patients with hormone-sensitive advanced prostate cancer, treatment with relugolix resulted in adequate, sustained castration up to approximately one year of treatment duration and demonstrated non-inferiority in terms of castration to standard of care treatment with another hormone agent (leuprolide). Relugolix has been generally well-tolerated in most studies in patients with advanced prostate cancer. The most common side effects with Orgovyx (which may affect more than 1 in 5 people) are hot flushes, muscle and joint pain and tiredness. Other very common side effects are diarrhea and constipation.

In summary, relugolix is the first oral hormone therapy that provides an advantage over current alternatives, whether agonists or antagonists, in terms of rapidly reducing testosterone levels, returning to normal levels, avoiding flare-ups, potentially reducing the risks of cardiovascular complications in patients with cardiovascular diseases compared to antagonists and ensuring the absence of undesirable local effects from the injection itself.

6.Companion Diagnostic Test

<Enter Response Here>

7.Anything Else?

In our view: Clinical and patient benefits and economic advantages:

- Rapid reduction of testosterone levels over an extended period (approximately one year)
- No need to manage flares (e.g., with Casodex for 30 days) $
- Faster return to normal after treatment cessation
- No pain at the injection site as the medication is oral
- Reduced stress for the nurse (less planning and preparation for injections) $
- Potentially fewer cardiovascular events (to be monitored) $

In summary, considering evaluations by various countries and the needs of our patients, relugolix can be deemed a valuable addition to the treatment options for advanced prostate cancer.

Appendix: Patient Group Conflict of Interest Declaration

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No

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   No

2. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

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The ADT Educational Program

1. About Your Patient Group

The ADT Educational Program [https://www.lifeonadt.com] supports prostate cancer patients undergoing hormone therapies (formally referred to as androgen deprivation therapy; ADT). The Program includes a 1.5-hour professionally facilitated class plus a book, *Androgen Deprivation Therapy: An Essential Guide for Prostate Cancer Patients and Their Loved Ones* published by Springer Health [See: https://www.springerpub.com/androgen-deprivation-therapy-9780826184023.html] With industry support, the Program is free for men in Canada prescribed ADT to control their prostate cancer.

Together, the single class and book cover evidence-based strategies for managing ADT side effects, such as fatigue, weight gain, muscle loss, osteoporosis, hot flashes, cardiovascular risk, depression, and sexual dysfunction. The Program is designed to educate patients about all ADT treatment side effects plus strategies to mitigating those side effects so they can remain healthy for the longest time possible. The program serves not just patients, but also their intimate partners and other family members.

2. Information Gathering

The genesis of the Program was a CIHR-funded conference held in Halifax, Nova Scotia in 2008. It was attended by researchers and healthcare provider from Canada and the USA, who work with prostate cancer patients challenged by the side effects of ADT. That led to a PhD thesis testing the hypothesis that patients could manage the side effects best, if informed about them ahead of time. The ADT Educational team has since published results confirming the hypothesis [See Wibowo et al. 2020 https://doi.org/10.1177/1557988319898991]. Patients indeed benefit most from knowing what to expect from ADT and less so, if they take the class when already burdened by ADT side effects.

Before COVID, the ADT Educational Program was offered as in-person classes at several major cancer centres across Canada; e.g., Vancouver Prostate Centre, Calgary Prostate Cancer Centre, Allan Blair Cancer Centre, Saskatoon Cancer Centre, Princess Margaret Cancer Centre (Toronto) and the Queen Elizabeth II Health Sciences Centre (Halifax). Because many prostate cancer patients live beyond the reach of these centres, a nationally online version of the facilitated classes was introduced in 2018 and has continued monthly ever since.

Since 2019 the ADT class has been taken by 709 Canadian patients plus 402 partners and other family members. Most of the patients, who have attended the class, had already started on ADT and some of them have been on various ADT drugs in combination. This has given the ADT Education team a chance to hear from hundreds of patients and their loved ones about all of the challenges they have experienced with ADT drugs, their administration, and their side effects.

3.Disease Experience

I am an advanced prostate cancer (PCa) patient, who has been on androgen deprivation therapy (ADT) almost continuously for over 20 years. I am a senior member of the ADT Working Group and the patient liaison for the Canada ADT Education Program. I am also the national Patient Representative for PCa on the Canadian Clinical Trials Group (CCTG) and have held that post for the last seven years. [See: Wassersug, 2021]. I am now charged with presenting the concerns of PCa patients about access to relugolix on behalf of the patients served by the Canada ADT Education Program.

As both a CCTG Patient Rep and the Patient Lead for the ADT Educational Program, I make a great effort to know the concerns of other PCa patients on ADT. To do this, I regularly participate in four national level (in both USA and Canada) PCa online zoom meetings and I follow daily several PCa chat groups.

Over the last fifteen years I have talked to hundreds of other PCa patients on ADT about their concerns with cancer and the side effects of treatment. I thus feel well informed about how PCa patients, who need androgen suppressing medications, feel about relugolix compared toother Health Canada approved options for ADT.

4.Experiences With Currently Available Treatments

All ADT drugs licensed in Canada are effective in controlling hormone sensitive PCa, but come with a wealth of side effects. The ones that we experience as patients that are most disturbing are hot flashes, fatigue, and loss of sexual interest. But we also regularly experience loss of muscle mass, yet weight gained as fat. This makes simply walking up a flight of stairs more difficult. Many of us find that the ADT drugs affect our ability to solve simple spatial problems on a variety of scales. This can range from losing one's car in a large parking lot to losing papers on a cluttered desk.

Collectively these side effects can lead to depression and insomnia. We feel weak, old, flabby, and demoralized. Many of us are on antidepressants and additional drugs to help us sleep through the night.

These side effects are so burdensome that I've talked to a several patients over the years (two in the last eight months), who have taken an initial injection of an ADT agent and found the side effects intolerable. They both vowed that they will not continue on the medication even though they have been advised to do so by their physicians.

In additions there are problems associated with the way the currently available ADT agents are delivered. These drugs are of two sorts: LHRH agonists and LHRH antagonists. They have similar side effects, and both are delivered through depot injection into the buttocks or the fat of the anterior abdominal wall. Depending on the specific drug, patients need new injections every one to six months.

The injections are not fun and can cause inflammation at the injection site which can be uncomfortable for many days after. As a result, there are patients who will start on the currently available ADT drugs but delay getting repeated injections or take risky drug holidays that can cause their cancer to fulminate.

The LHRH antagonist currently available in Canada is degarelix (Firmagon). For patients with newly diagnosed PCa that is metastatic—who need to depress their testosterone quickly—the one drug that does that is degarelix. It is also the drug most similar to relugolix. Both drugs have the advantage over the LHRH agonists in be quick acting and supposedly safer for patient with pre-existing cardiovascular disease. However, when patients start on degarelix, they need two injections, not one, and they need a new injection each month after that.

I have not personally been on degarelix, but I've talked to MANY patients, who have had major discomfort from the injections that lasted for days. Relugolix gets around problems with the injections because it is an oral medication. In my discussions with patients in the USA currently on relugolix, they all feel pleased that they do not have to go through the pain and inconvenience of the depot injections.

As with the other Health Canada approved ADT agents, for PCa patients with symptomatic metastatic disease, relugolix would reduce the severity of PCa symptoms, minimize adverse effects of the cancer, and help maintain health related quality of life. Bit its profound advantage is simply that it is an oral drug which makes it far more tolerable to patients and more likely to have better compliance.

As an oral drug, relugolix will improve compliance, particularly for patients who already take other oral medications on a daily basis. Relugolix will also be psychologically easier to tolerate because it requires no injections.

5.Improved Outcomes

From a patient’s perspective, it is profoundly better to start one’s cancer treatments with an oral drug rather than with an uncomfortable bolus injection or more radical treatments. such as surgery or radiotherapy. For a patient, who is newly diagnosed with advanced cancer and needs to start treatment fast, the drug that is most appropriate now is the other LHRH antagonist, degarelix. Since degarelix and relugolix are very similar, it may seem that the existing treatment is adequate and there is not a great value in offering an oral alternative. But from the psychological perspective, there is an enormous difference. When a patient learns that they have cancer—and think of people they know challenged by chemotherapy, radiation, and surgery—they immediately envision a loss of both quality and quantity of life. Getting difficult injections from the start inspires morbid thinking about what further treatments might be like. As a result, many patients delay or decline getting the injections.

An oral drug alleviates much of this problem. Most men in the age group that are diagnosed with advanced cancer are already taken medications to manage their cardiovascular or diabetic risk. In that regard they understand that oral medications can be used as maintenance drugs and do not necessarily indicate that

aggressive and difficult treatments are inevitable. By offering patients an oral ADT agent as an initial agent for androgen suppression, patients can perceive of this as a maintenance treatment and not necessarily the beginning of progressively more challenging treatments.

To the extent that men easily learn to take a daily statin drugs to manage cholesterol or metformin to manage diabetic risk, relugolix can justifiably been seen as a maintenance drug. This is an incredibly valuable positive mindset for these patients… and it is truly realistic. It is increasingly common for patients to have long term survival with ADT, but in order to maintain a good quality of life they need to think of this as maintaining their quality of life and not a difficult, invasive, cancer treatment.

To the extent that these PCa patients on an ADT agent can come to see themselves as living with a cancer rather than dying of it, it can be inspirational not just for themselves, but for other cancer patients, who have good prospects for long-term survival.

In sum it may seem a minor point that relugolix is an oral drug and not an injected medication. But this is a profoundly positive difference for the patients…and a major advance in prostate cancer care. Please authorize relugolix for sale in Canada!

6.Experience With Drug Under Review

I've not yet heard from any patients, who are on relugolix and would prefer to be on the depot injections for ADT. As a new drug, I would expect relugolix to be expensive when it first comes on the market in Canada. But one has to factor in the cost of clinical staff to administer the injections when doing a cost comparison.

I have sadly heard from many patients who delayed getting ADT injections during COVID because they feared catching COVID at the clinic where they would normally get their ADT injections. This suggests that compliance with relugolix will be higher than any of the injectable LHRH drugs as it would require no in-person clinical visits. That will a major emotional benefit for us patients. And, in the long run, it will be a benefit for the cancer centre staff as well, who are overworked everywhere in Canada right now.

I've not attempted to survey patients, who have started on relugolix in the USA, and then elected to go over to depot injection drugs. I have also not heard of any patients, who found that taking relugolix was a challenge to compliance. The fact is that most patients in our age group are taking daily oral medications, such as statin drugs, and it is easy to add in another oral drugs with the daily medications we currently take.

In sum as an advanced PCa patient, having access to relugolix, would make our cancer treatment far more manageable and humane.

If you need me to expand upon any of the above comments either from by personal perspective or for the hundreds of other PCa patients on ADT that I work with and care about, please feel free to get back to me.

7.Companion Diagnostic Test

Not applicable.

8.Anything Else?

Nope.

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   As noted above the ADT Educational Program is supported by companies that market drugs to treat prostate cancer. The current funders of the ADT Educational Program in Canada and their oncologically relevant agents are: XXXXXXX (Eligard = leuprolide), XXXXXXX (Pluvicto= lutetium vipivotide tetraxetan), XXXXXXX (Nubeqa= darolutamide) plus XXXXXXX and XXXXXXX (Xtandi= emzalutamide). Of the companies that support the ADT Education Program, the most direct competitor to Sumitomo Pharma's drug relugolix is XXXXXXX drug, Eligard. However, Eligard is an LHRH agonist and relugolix is an LHRH antagonist. These drugs work through the same gonadal-hypothalamic-pituitary axis to suppress the signal from the pituitary to the testes to produce testosterone. As a result, they with have the same suite of side-effects from androgen suppression.

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XXXXXXX		X		
XXXXXXX		X		
XXXXXXX			X	
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The Canadian Cancer Society (CCS)

1.About Your Patient Group

The Canadian Cancer Society (CCS) works tirelessly to save and improve lives. CCS is the only national charity that supports Canadians with all cancers in communities across the country. We fund the brightest minds in cancer research. We provide a compassionate support system for all those affected by cancer, from coast to coast and for all types of cancer. As the voice for Canadians who care about cancer, we work with governments to establish health policies to prevent cancer and better support those living with the disease. More information about CCS can be found here: Canadian Cancer Society . CCS used Hill and Knowlton Strategies to support coordination of this submission.

2. Information Gathering

CCS reached out to key stakeholders in the prostate cancer community with a call-out for patients and caregivers to provide patient input for this submission. One participant responded to the call-out who was interviewed in Canada. The participant is in British Colombia and 76 years of age. The patient had experience with the disease only—he did not have experience with Relugolix, the drug under review.

3. Disease Experience

The patient was 55 years of age when he was diagnosed with advanced prostate cancer. His caregiver is/was his wife, who didn't have a significant impact on her life, outside of the limited sexual desire he felt from the side effects of the treatment. He recognized the importance of controlling cancer and had to manage the side effects of the ADT treatment. Side effects of note included: weight gain, impact on kidneys and liver and reduced sexual desire. The patient mentioned no sexual desire as a key side effect, noting that the treatment killed his testosterone levels and a male without testosterone is "like a female".

He also noted that he had to start taking other medications to limit the impact of treatment on his kidneys, which was challenging. He was retired during the treatment and felt very weak and tired. He noted that he knew exercise was good for him, but the treatment made him feel weak and tired, limiting his motivation to exercise.

4. Experiences With Currently Available Treatments

The patient noted that he had no barriers in accessing treatment. Overall, he didn't have any challenges with cost, travel to clinic and time off work. Since he was retired, he didn't have to take time off work. He was also provided a reduced price at the lodges, with a free ride to Victoria. He did express concern with how quickly the treatment began, noting that he would prefer to have more time to process the information prior to beginning treatment.

5.Improved Outcomes

He wasn't sure what could be done but pointed to castration as an almost better solution. He expressed that the worst thing about the drug is killing off the testosterone – and could be something the drug could work to improve. The drugs also give more side effects than just the loss of the testosterone – which results in needed alternative drugs to address the side-effects from the treatment for prostate cancer.

He didn't feel like he had much say in his treatment and therapy. On the day he found out, he got an injection and drug, and then radiation for the prostate. He is grateful to be alive to this day (was diagnosed in 2002). He still has residual cancer and his PSA reading is increasing slowly.

6.Experience With Drug Under Review

The patient did not receive relugolix.

7.Companion Diagnostic Test

The patient found out about his cancer through a complete routine physical exam he completed at his doctor's clinic at the insistence of his wife. He did not feel any anxiety about the decision or the test. There was a clear path forward and he followed the recommendations of the experts. The biopsy was positive and then immediately after, his treatment began.

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Clinician Group Input

British Columbia Genitourinary Group with Vancouver Prostate Centre

1.About Your Clinician Group

The BC Genitourinary Tumor Group consists of medical oncologists, radiation oncologists and urologic oncologists from across the province. This body advises the leadership of BC Cancer, the regional health authorities, the provincial Ministry of Health and other stakeholders on all matters related to the care of patients with genitourinary cancers, including especially prostate, bladder and kidney cancer.

The Vancouver Prostate Centre (https://www.prostatecentre.com/) is hosted by the Vancouver Coastal Health Research Institute and the University of British Columbia. It is one of the world's premier prostate cancer research institutions that spans the spectrum of basic, translational and clinical research. Care of all patients with genitourinary cancers at Vancouver General Hospital is conducted through the Vancouver Prostate Centre, which houses also an active clinical trials unit.

2.Information Gathering

Peer-reviewed publications.

3.Current Treatments and Treatment Goals

Relugolix can be used for the same indications as the established agents for androgen deprivation therapy (ADT). These agents include various luteinizing hormone releasing hormone (LHRH)-agonists (e.g. leuprolide or goserelin) and an LHRH-antagonist (degarelix) that are administered by subcutaneous or intramuscular injection. The indications for ADT include (PubMed ID provided for one review paper on each indication):

1) Concomitant ADT with definitive radiation therapy for localized prostate cancer (PMID: 32146018). In high-risk prostate cancer this can be combined with abiraterone, which is a new treatment option that is not yet widely funded.

2) Concomitant ADT with adjuvant/salvage radiation therapy after prior radical prostatectomy for localized prostate cancer (PMID: 32852528).

3) Intermittent or continuous ADT (monotherapy) for biochemical recurrence after definitive local therapy (PMID: 35641398). When this transforms to castrate-resistant non-metastatic prostate cancer, ADT can be combined with an androgen receptor pathway inhibitor.

4) ADT for treatment of metastatic prostate cancer (castrate sensitive and castrate resistant) (PMID: 36656694) in combination with other systemic agents such as androgen receptor pathway inhibitors, docetaxel, radioligand therapy and PARP inhibitors. In patients with oligometastatic castrate sensitive prostate cancer, the primary cancer is often treated with radiation therapy. There is an increasing trend to treat sites of metastasis or recurrence in oligometastatic or oligorecurrent prostate cancer with stereotactic radiation.

All of these systemic therapies are approved by Health Canada. Treatments described under 1 and 2 are administered with curative intent. Treatment described under 3 and 4 prolong survival and increase quality of life but are not generally curative.

Bilateral orchiectomy remains an option for men on continuous, permanent ADT, but the vast majority of men elect medical over surgical castration.

4.Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Relugolix would replace any of the LHRH agonists or degarelix in the indications described above. It provides several advantages:

1. Relugolix represents the only LHRH agonist/antagonist that can be administered orally rather than by subcutaneous or intramuscular injection. This is particularly important when comparing relugolix to degarelix since both are LHRH antagonists. Degarelix requires frequent injection (monthly as opposed to every 3-6 months for LHRH antagonists) and is associated with injection site reactions. Degarelix injections are high volume (6 ml for loading dose and 4 ml for maintenance doses). Oral dosing is particularly advantageous for patients who live remotely or have difficulties commuting to a healthcare delivery site. It is also advantageous for patients who travel south for the winter.

2. LHRH antagonists are preferred over LHRH agonists in the immediate treatment of men with a new diagnosis of metastatic prostate cancer because the antagonist leads to a more rapid suppression of serum testosterone. This is therefore the safest treatment with the most rapid relief of symptoms.

3. LHRH antagonists are preferred over LHRH agonists in men with prostate cancer and existing cardiovascular disease or risk factors for the same. Retrospective pooled analysis of 6 prospective phase III clinical trials suggests that the LHRH antagonist degarelix is associated with fewer cardiovascular complications than the LHRH agonist leuprolide, especially in patients with existing cardiovascular disease or risk factors (PMID 24210090). This holds up also in a systematic review (PMID:33470403). A prospective, randomized, open-label trial was conducted in men with prostate cancer and cardiovascular disease to verify if degarelix reduced the rate of major adverse cardiovascular events compared to an LHRH agonist, but the trial failed to accrue adequately, and the event rate was lower than anticipated (PMID 34459214). Patients in both arms of the trial received cardio-oncologic care, which may have contributed to the low event rate. The trial failed to show a difference between both types of ADT with respect to the primary endpoint.

4. LHRH antagonists would be preferential to LHRH agonists in men with localized prostate cancer receiving temporary ADT to potentiate the effects of radiation therapy because the testosterone recovers more rapidly after discontinuation of the therapy, with resultant more rapid resolution of associated symptoms (e.g. fatigue, hot flashes and impaired libido).

5.Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Relugolix would be used as a substitute for any LHRH agonist or degarelix in any disease state in which these drugs are indicated.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All patients requiring ADT can receive relugolix. If there is a concern about patient compliance, a 3-, 4- or 6-month depot injection of an LHRH agonist may be preferential. The patients who might benefit most from relugolix are those described above (patients who have difficult access to injection clinics, patients with newly diagnosed metastatic prostate cancer requiring immediate treatment effect, and patients on short-term ADT in who rapid recovery of testosterone is desirable after discontinuation). Rapid treatment effect in patients with newly diagnosed prostate cancer is particular important if there is widespread bony involvement causing pain or imminent risk of spinal cord compression or if there is locally advanced tumor causing urinary retention and/or ureteral obstruction.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Treatment response will not differ if using relugolix versus other existing ADT options. Serum testosterone is measured periodically to ensure adequate suppression, which is the primary pharmacodynamic readout of the treatment. Serum PSA is measured periodically to measure impact of treatment on prostate cancer growth. In patients with metastatic or locally advanced prostate cancer, imaging studies, including CT, bone scan and PSMA-PET scanning, are used for baseline assessment and periodically based on PSA kinetics to assess disease burden. Treatment response is measured primarily by PSA suppression in patients with non-metastatic disease, and by clinical assessment, PSA and imaging in patients with metastatic disease.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

ADT is generally never discontinued in patients with metastatic or locally advanced prostate cancer. It can be administered intermittently based on PSA kinetics in patients with biochemical recurrence. It is administered for a pre-determined duration of time in patients receiving ADT with curative-intent radiation.

5.5 What settings are appropriate for treatment with drug under review? Is a specialist required to diagnose, treat, and monitor patients who might receive drug under review?

This is an oral medication that will be provided by BC Cancer pharmacies in the outpatient setting under the supervision of a urologist, radiation oncologist or medical oncologist.

6.Additional Information

Not applicable.

7.Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

None

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

None

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1

Name: Peter Black

Position: Professor, Department of Urologic Sciences, University of British Columbia; Associate Director, Clinical Research, Vancouver Prostate Centre; Chair, Surgery Subcommittee, BC Cancer GU Tumour Group.

Date: 19-11-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Tersera (goserelin)	X			
Tolmar (leuprolide)	X			
Abbvie (leuprolide)	X			
Sumitomo (relugolix)	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Scott Tyldesley

Position: Radiation Oncologist, BC Cancer (Vancouver); Clinical Professor, Department of Surgery UBC

Date: 19-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Tolmar	X			
Tersera	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Martin Gleave

Position: Professor and Department Head, Department of Urologic Sciences, UBC; Executive Director, Vancouver Prostate Centre; Former Chair, BC GU Tumor Group

Date: 19-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Krista Noonan

Position: Medical Oncologist, BC Cancer (Fraser Valley); Chair, Systemic Therapy Subcommittee, BC GU Tumor Group

Date: 19-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Tersera	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Michael Peacock

Position: Radiation Oncologist, BC Cancer (Vancouver); Clinical Assistant Professor, Department of Surgery, UBC

Date: 19-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Tersera	X			
Abbvie	X			
Tolmar	X			
Sumitomo	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Alan So

Position: Associate Professor, Department of Urologic Sciences, UBC; Senior Research Scientist, Vancouver Prostate Centre; Former Head, BC GU Tumor Group

Date: 19-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sumitomo	X			

* Place an X in the appropriate dollar range cells for each company.

The ADT Educational Program

1.About Your Clinician Group

The ADT Educational Program [https://www.lifeonadt.com] supports prostate cancer (PCa) patients undergoing hormone therapies (formally referred to as androgen deprivation therapy; ADT). The Program includes a 1.5-hour professionally facilitated class plus a book, Androgen Deprivation Therapy: An Essential Guide for Prostate Cancer Patients and Their Loved Ones published by Springer Health [See: https://www.springerpub.com/androgen-deprivation-therapy-9780826184023.html] With industry support, the Program is free for men in Canada prescribed ADT to control their PCa.

Together, the single class and book cover evidence-based strategies for managing ADT side effects, such as fatigue, weight gain, muscle loss, osteoporosis, hot flashes, cardiovascular risk, depression, and sexual dysfunction. The Program is designed to educate patients about all ADT treatment side effects plus strategies to mitigating those side effects so they can remain healthy for the longest time possible. The program serves not just patients, but also their intimate partners and other family members.

2. Information Gathering

The genesis of the Program was a CIHR-funded conference held in Halifax, Nova Scotia in 2008. It was attended by researchers and healthcare provider from Canada and the USA, who work with PCa patients challenged by the side effects of ADT. That led to a PhD thesis testing the hypothesis that patients could manage the side effects best, if informed about them ahead of time. The ADT Educational team has since published results confirming the hypothesis [See Wibowo et al. 2020 https://doi.org/10.1177/1557988319898991]. Patients indeed benefit most from knowing what to expect from ADT and less so if they take the class when already burdened by ADT side effects.

Before COVID, the ADT Educational Program was offered as in-person classes at several major cancer centres across Canada; e.g., Vancouver Prostate Centre, Calgary Prostate Cancer Centre, Allan Blair Cancer Centre, Saskatoon Cancer Centre, Princess Margaret Cancer Centre (Toronto) and the Queen Elizabeth II Health Sciences Centre (Halifax). Because many PCa patients live beyond the reach of these centres, a nationally online version of the facilitated classes was introduced in 2018 and has continued monthly ever since.

Since 2019 the ADT class has been taken by 709 Canadian patients plus 402 partners and other family members. Most of the patients, who have attended the class, have already started on ADT and some of them have been on various ADT drugs in combination. This has given the ADT Education team a chance to hear from hundreds of patients and their loved ones about all of the challenges they have experienced with ADT drugs, their administration, and their side effects.

3.Current Treatments and Treatment Goals

Our comments below all pertain to the ADT treatment currently available in Canada with Health Canada approval.

Newly diagnosed patients with advanced PCa are commonly started on androgen suppressing medications. These include LHRH agonists and LHRH antagonists. Those drugs may be used in combination with second-generation anti-androgens (e.g., enzalutamide, apalutamide, and darolutamide) or the androgen synthesizing blocking drug abiraterone. The primary agent is always an LHRH agonist or antagonist. The antagonist, degarelix, is the drug of

choice for patients, who are diagnosed with symptomatic metastasises because it suppresses testosterone quicker than the LHRH agonists, which initially cause a flare in testosterone.

The only alternative to these drug treatments is surgical castration. An orchiectomy is an acceptable treatment in Canada, but is not reversable like the LHRH drugs, and many patients (and clinicians) consider the surgery more invasive and traumatic than medical castration, so it is rarely used in Canada.

All of the LHRH drugs massively suppresses testosterone production from the testes, but cause a large array of side effects. These are covered in detail—as well as strategies for managing them—in the book Androgen Deprivation Therapy: An essential guide for prostate cancer patients and their loved ones [https://www.springerpub.com/androgen-deprivation-therapy-9780826184023.html].

One of the most important goals that an ideal PCa treatment would address is simply to be curative for symptomatic PCa. Sadly, once the disease has spread past the gland it is non-curative. At that point, the single best and well-established treatment is androgen suppression with LHRH drugs. However, the administration of these drugs is difficult because they require repeated bolus injections that can be uncomfortable for days to weeks depending on how they are administered and the tissue they are injected into. Thus, an important goal is to develop agents that can cause androgen suppression with either less side effects or less invasive administration. The drug under consideration here, relugolix, is particularly valuable because it is a simple oral drug that is easier for patients to manage then repeated bolus injections.

Relugolix has a profound advantage compared to the other primary ADT drugs currently available in Canada, simply because it is an oral drug, which makes it far more tolerable to patients.

4.Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The new drug considered here explicitly addresses the need for a treatment that is better tolerated and improves compliance. It is also more convenient for both patients and clinicians because it does not require injections by specialist nurses. The current treatments now are depo-injections of androgen suppressing agents that are uncomfortable, scary to some patients, and many find simply intolerable. As a result, there are patients who will start on the currently available ADT drugs but delay getting repeated injections or take risky drug holidays which can lead to disease progression.

A simple oral drug can easily improve compliance, particularly for patients who already take other medications on a daily basis. Relugolix is psychologically easier to tolerate because it require no injections.

A major barrier to current ADT treatments for suppressing testosterone production in the testes is the size of the bolus that needs to be injected when these drugs are administered. The one drug that is best suited for treating de novo metastatic prostate cancer is the LHRH antagonist, degarelix, but degarelix has been shown to lead to the greatest amount of inflammation and discomfort at the injection site. As a result, many patients start on degaralix then shift to an LHRH agonist, however all LHRH agonist drugs that are health Canada approved also require large bolus injections that are still uncomfortable.

5.Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Increasingly the standard ADT agents are being used in combination with anti-androgens or abiraterone. The new drug could similarly be used in combination with those drugs. The add-on drugs are also oral medications so this would require no special injections, if those drugs are added to relugolix for combination therapy.

Relugolix is not the first drug used for androgen suppression nor does the literature at this point suggest that it would be particularly better than the currently available ADT agents for oncological or side effect management. The big difference with relugolix compared to its predecessors is, as noted elsewhere, that it is an oral medication. However, that is a profoundly valuable shift considering the difficulty that patients have with the current drugs e approved for androgen deprivation, which are all depo-injections.

The drug would be used as a first-line treatment. It is possible that the medication could be reserved for patients. who find the injection of the LHRH agonists especially distressing, and avoid or delay ADT. If these are metastatic patients that must start promptly, without delay. For them, taking an oral drug would be much easier and quicker for starting treatment.

From the increasing popularity in the United States since getting FDA approval, relugolix has indeed caused a shift in treatment paradigm for patients who are newly diagnosed with metastatic cancer and need to start ADT promptly . A limiting factor in Canada would of course be cost, but as the drug becomes more commonly used, we can expect it to also become cheaper. Right now, patients who want to go on the drug, and can afford it, can go down to the United States to get it. The money they spend there is lost to the health care system.

We would be inclined to advise any new patient we talk to, who needs to go on ADT, to explore all options for getting relugolix. Obviously though it would be better, if they could get access without having to leave the country.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As with other ADT agents, in addition to treating systemic disease, relugolix would be appropriate for patients, who need ADT short-term as adjuvant to radio-therapy. However, the primary market would be patients with de novo metastatic cancer. For patients, who have hormone sensitive systemic disease, the drug would be an excellent first line ADT agent.

The patients, who are most likely to benefit from this drug, are those who present with substantial metastatic disease. Those are the patients, who are most in need of prompt androgen suppression. The distinction as to who would be best patients to start ADT with relugolix depends on their metastatic status. That requires adequate imaging, which has improved in recent years with the availability of radionuclide PSMA PET scans.

As with the currently available ADT agents, the effectiveness of relugolix in controlling PCa would be assessed with either bio-chemical progression (rising PSA) or progression on diagnostic imaging.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

We do not envision any changes in assessing response to treatment with relugolix that would be different from current practices in assessing treatment outcomes from patients on any of the already available ADT medications.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Given current treatment protocols no patients with castrate resistant metastatic prostate cancer should stop taking an LHRH drug unless it is counter indicated by other comorbidities or excludes them from clinical trials that might wish to join.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Patient starting on this drug will most commonly have a diagnosis of systemic prostate cancer confirmed with appropriate imaging of being offered it as adjuvant of high list localized disease being treated with radiotherapy. {Patients with systemic disease need continuous monitoring for disease progression and should be in the care of an uro-oncologist.

6.Additional Information

In order to appreciate the challenges of managing patients on ADT we refer you to the following paper recently published in Urology Practice [https://www.auajournals.org/doi/epdf/10.1097/UPJ.0000000000000473].

7.Conflict of Interest Declarations

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No.

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As noted above the ADT Educational Program is supported by companies that market drugs to treat prostate cancer. The current funders of the ADT Educational Program in Canada and their oncological relevant agents are: Tolmar (Eligard = leuprolide), Novartis (Pluvicto= lutetium vipivotide tetraxetan), Bayer (Nubeqa= darolutamide) plus Astellus and Pfizer (Xtandi= enzalutamide). Of these, the most direct competitor to Sumitomo Pharma’s drug relugolix is

Tolmar's drug, Eligard, but it an LHRH agonist whereas relugolix is an LHRH antagonist. Like the other ADT agents, both the agonists and the antagonist work through the gonadal-hypothalamic-pituitary axis to suppress the signal from the pituitary to the testes to produce testosterone. As a result, they with have the same large suite of side-effects from androgen suppression.

Declaration for Clinician 1

Name: Lauren Walker

Position: Clinical Psychologist

Date: <13-11-2023>

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

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Tolmar			X	
Novartis		X		
Bayer		X		
Astellas			X	
Pfizer		X		

* Place an X in the appropriate dollar range cells for each company.